THE Journal of the Kansas Medical Society

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Volume LXI, Number 3—March, 1960

The JOURNAL of the KANSAS MEDICAL SOCIETY

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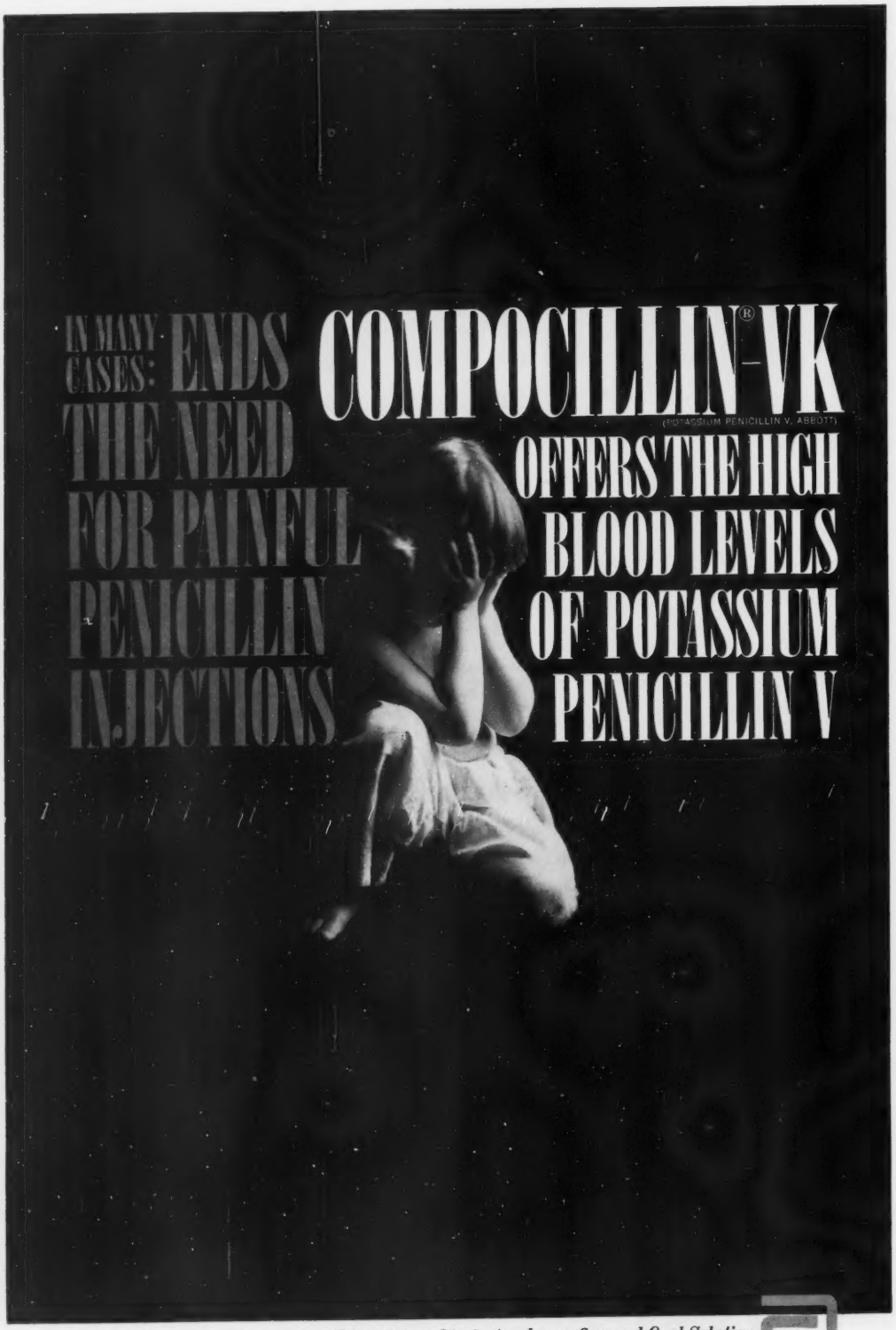

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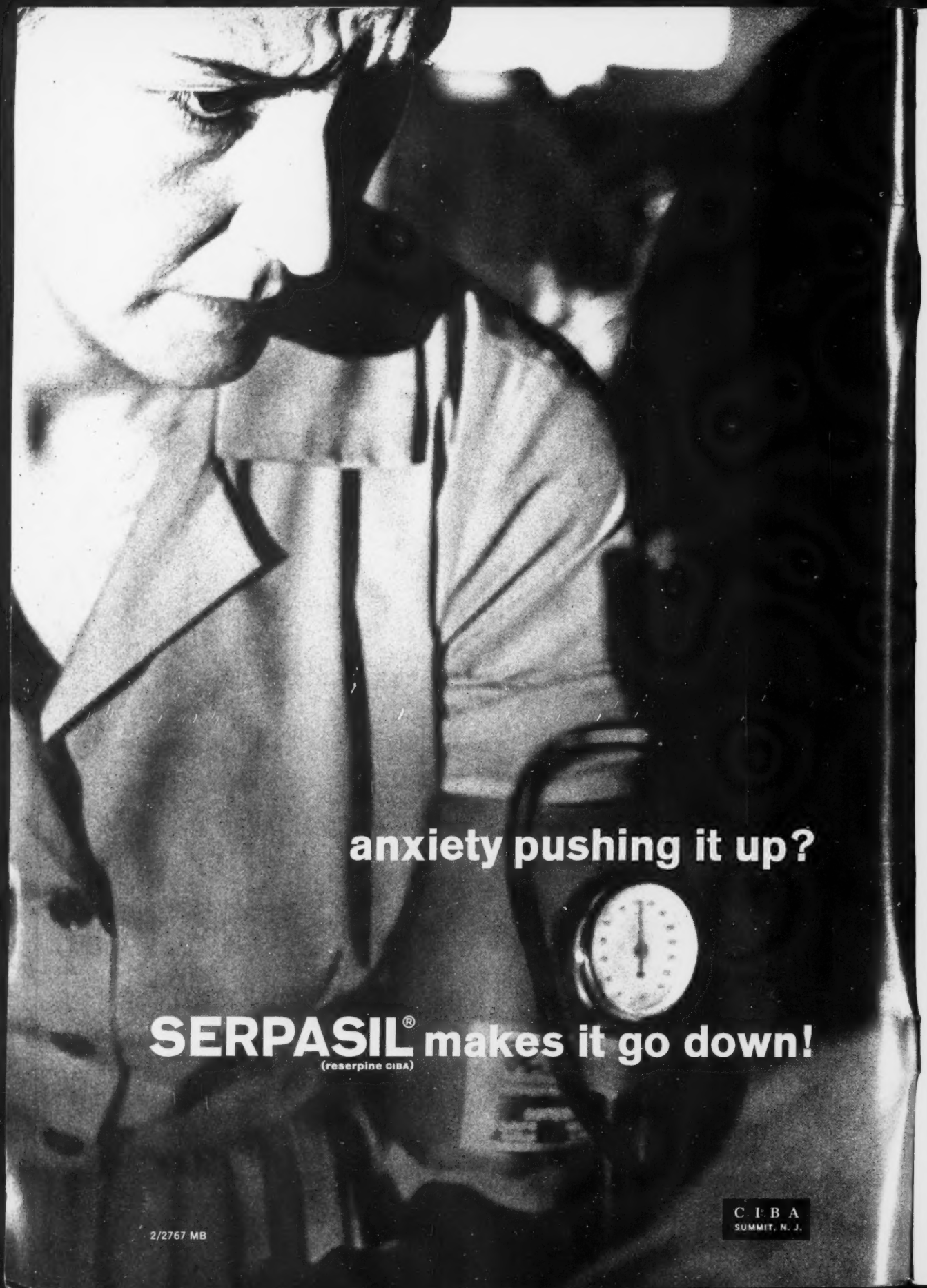
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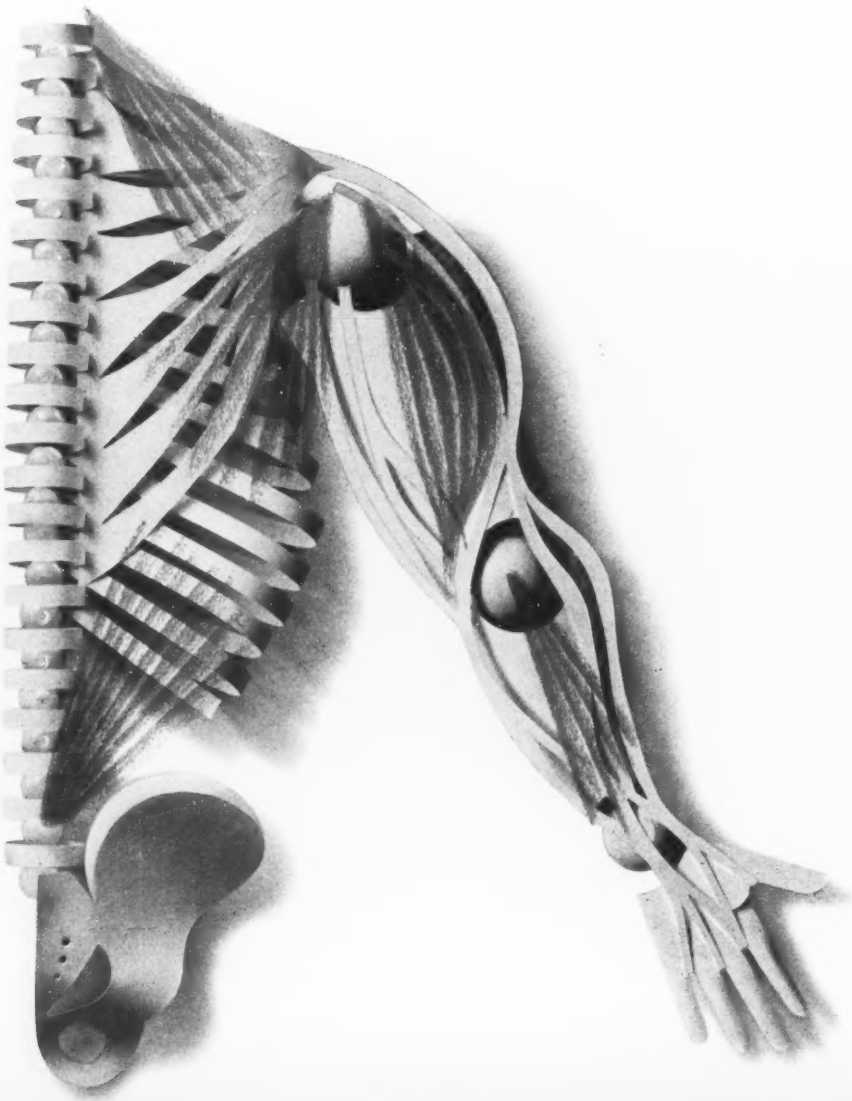

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Cooper, C. D., and Epstein, J. H.: The Clinical Evaluation of Carisoprodol by a double-blind technique. Ibid. p. 97.

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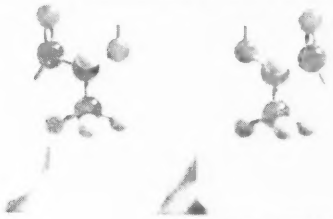

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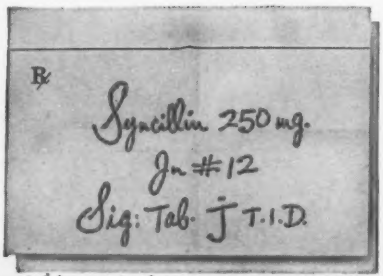
Efficacy of SYNCILLIN against staphylococci and other resistant organisms

Studies have shown that SYNCILLIN is effective *in vitro* against 60 to 75% of hospital "staph" strains, while penicillin G and penicillin V are now effective against only 30 to 50%.[1, 2] Therefore, if clinical judgment indicates the use of penicillin, SYNCILLIN would be expected to be the most effective. However, since some strains are still resistant to SYNCILLIN as well as to the other penicillins, cultures and sensitivity tests should be performed where indicated by clinical judgment.

There have recently been reports of decreased efficacy of penicillin in streptococcal[3] and gonococcal[4, 5] infections. The emergence of penicillin-resistant gonococci appears to be associated with an increase in the incidence of gonorrhea all over the world. When a less sensitive strain is encountered the higher blood levels produced by SYNCILLIN may be most helpful.



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Relation of intermittent high blood levels of SYNCILLIN to antibacterial efficacy

SYNCILLIN, like all clinically available penicillins, is bactericidal. Periodic high blood concentrations may be sufficient to permit complete eradication of sensitive pathogens. According to Eagle,[6] "Soon after penicillin attains effective concentrations, the bacteria cease multiplying; and the bacteriostatic effect persists for a number of hours after penicillin has fallen to concentrations that are wholly ineffective. . . . The therapeutic significance of this postpenicillin recovery period is enhanced by the fact that the recovering bacteria, damaged but not killed by the previous exposure to penicillin, are abnormally susceptible to the host defenses. In consequence, the bactericidal process *in vivo* continues for many hours after the drug itself has fallen to ineffective concentrations."

Reduced rate of inactivation of SYNCILLIN by staph penicillinase

Bacterial resistance to penicillin has been attributed to the action of penicillin-inactivating enzymes produced by the invading organisms. SYNCILLIN is less affected by staphylococcal penicillinase than either of its component isomers. Further, SYNCILLIN is shown to be less inactivated by this enzyme than penicillin V or penicillin G. Penicillinase from *B. cereus* likewise inactivates SYNCILLIN less rapidly than penicillin V or G.

Indications: SYNCILLIN is recommended in the treatment of infections caused by pneumococci, streptococci, gonococci, corynebacteria, and penicillin-sensitive staphylococci. In addition, SYNCILLIN is effective against certain strains of staphylococci resistant to other penicillins. SYNCILLIN, like other oral penicillins, is not recommended at the present time in deep-seated or chronic infections, subacute bacterial endocarditis, meningitis, or syphilis.

Dosage: 125 mg. or 250 mg. three times daily, depending on the severity of infection. Larger doses (e.g., 500 mg. t.i.d.) may be used for more severe infections. SYNCILLIN may be administered without regard to meals. Beta hemolytic streptococcal infections should be treated with SYNCILLIN for at least ten days.

Precautions: At the present time it is not possible to draw definite conclusions regarding the incidence of allergenicity to SYNCILLIN or its cross-allergenicity with natural penicillins. *Therefore, the usual precautions for oral penicillin therapy should always be observed.* Patients with histories of asthma, hay fever, urticaria, or previous reactions to penicillin should be watched with special care. Administration of oral penicillin, in rare instances, may provoke acute anaphylaxis, particularly in penicillin-sensitive individuals.

Diarrhea has been reported occasionally following heavy dosage. If this occurs, lengthen the interval between dosages.

If superinfection occurs during therapy, appropriate measures should be taken. Since some strains of staphylococci are resistant to SYNCILLIN as well as to other penicillins, cultures and sensitivity tests should be performed where indicated by clinical judgment. As is true with all antibiotics, clinical response does not always correlate with laboratory bacterial sensitivity reports.

Supply: 125 and 250 mg. tablets, bottles of 25 and 100. 125 mg. powder for oral solution, 60 ml. vials.

References: 1. Wright, W. W.: Microbiology Report to Bristol Laboratories Inc. 2. Morigi, E. M. E.; Wheatley, W. B., and Albright, H.: Paper presented at the Seventh Antibiotic Symposium, November 4-6, 1959, Washington, D.C. 3. Editorial: New England J. Med. **261**:305 (Aug. 6) 1959. 4. King, A.: Lancet **1**:651 (March 29) 1958. 5. Epstein, E.: J.A.M.A. **169**:1055 (March 7) 1959. 6. Eagle, H. and Musselman, A. D.: J. Bact. **58**:475, 1949.

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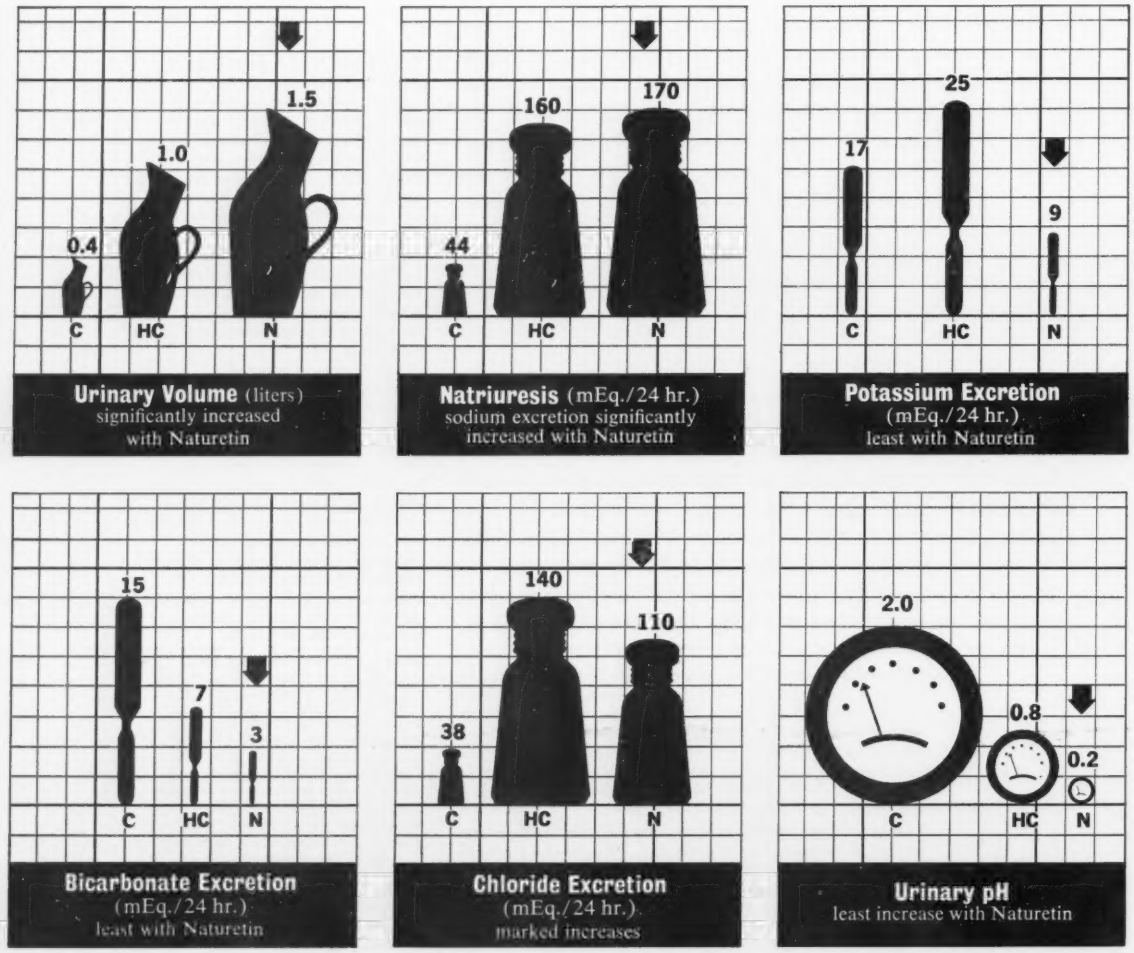
Comparison of electrolyte excretion pattern for the 24 hours following typical doses of chlorothiazide, hydrochlorothiazide, and Naturetin[1]



Typical Doses: Chlorothiazide—1,000 mg.; Hydrochlorothiazide—50 mg.; Naturetin (Benzydroflumethiazide)—5 mg.

1. Adapted from: Ford, R. V., Squibb Clin. Res. Notes 2:1 (Dec.) 1959.

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- prolonged action – in excess of 18 hours
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- comparative studies with chlorothiazide, hydrochlorothiazide, and Naturetin disclose that smallest doses of Naturetin produce greater weight loss per day
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- purpura and agranulocytosis not observed
- allergic reactions rarely observed

[2]Reports (1959) to the Squibb Institute for Medical Research.

Naturētin –*Indications:* in control of edema when diuresis is required, in congestive heart failure, in the premenstrual syndrome, nephrosis and nephritis, cirrhosis with ascites, edema induced by drugs (certain steroids); in the management of hypertension, used alone, combined with Raudixin (Squibb Rauwolfia Serpentina Whole Root), or with other antihypertensive drugs, such as ganglionic blocking agents.

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Precautions: when Naturetin is added to an antihypertensive regimen including hydralazine, veratrum, and/or ganglionic blocking agents, immediate reduction must be made in the dosage for all preparations; the dosage for ganglionic blocking agents must be decreased by 50% to avoid a precipitous drop in blood pressure. This also applies if these hypotensive drugs are added to an established Naturetin regimen . . . in hypochloremic alkalosis with or without hypokalemia . . . in cirrhotic patients or those on digitalis therapy when reductions in serum potassium are noted . . . in diabetic patients or those predisposed to diabetes . . . when increased uric acid concentrations are noted . . . when signs—leg or abdominal cramps, pruritus, paresthesia, rash—suggestive of hypersensitivity, are noted.

Naturētin –*Dosage: in edema,* average dose, 5 mg., once daily, preferably in the morning; to initiate therapy, up to 20 mg., once daily or in divided doses; for maintenance, 2.5 to 5.0 mg., daily in a single dose. *In hypertension:* suggested initial dose, 5 to 20 mg. daily; for maintenance, 2.5 to 15 mg. daily, depending on the individual response of the patient. When Naturetin is added to an antihypertensive regimen with other agents, lower maintenance doses of each drug should be used.

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1. Projection from Vital Statistics, U.S. Government Dept. HEW, Vol. 48, No. 14, 1958, p. 398.
2. Modell, W.: Drugs of Choice 1958-1959, St. Louis, C. V. Mosby Company, 1958, p. 347.

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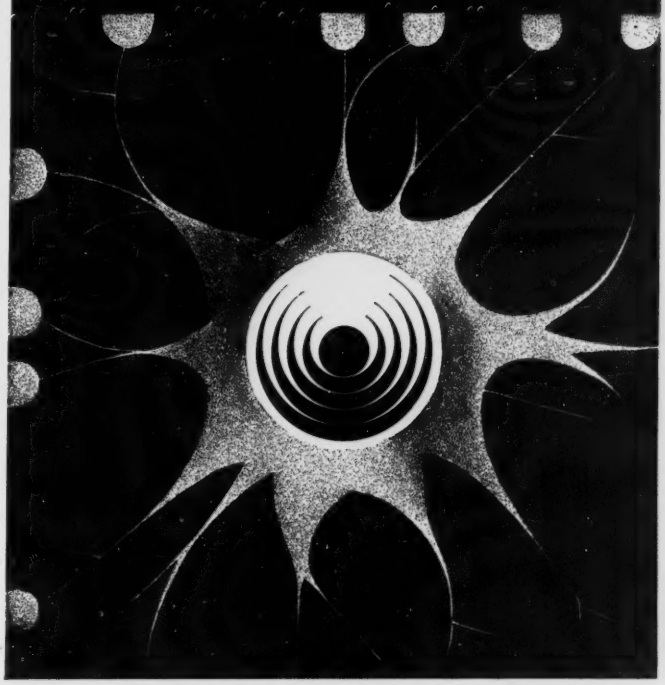
Tofrānil®

brand of imipramine HCl

in depression

lights the road to recovery
in 80 per cent of cases



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a potent thymoleptic . . .
not a MAO inhibitor.

Does act effectively in *all* types of depression regardless of severity or chronicity.

Does not inhibit monoamine oxidase in brain or liver; produce CNS stimulation; or potentiate other drugs such as barbiturates and alcohol.

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Tofrānil® brand of imipramine HCl: tablets of 25 mg., bottles of 100. Ampuls for intramuscular administration only, each containing 25 mg. in 2 cc. of solution, cartons of 10 and 50.

References: 1. Ayd, F. J., Jr.: Bull. School Med., Univ. Maryland *44*:29, 1959. 2. Azima, H., and Vispo, R. H.: A.M.A. Arch. Neurol. & Psychiat. *81*:658, 1959. 3. Lehmann, H. E.; Cahn, C. H., and de Verteuil, R. L.: Canad. Psychiat. A. J. *3*:155, 1958. 4. Mann, A. M. and MacPherson, A. S.: Canad. Psychiat. A. J. *4*:38, 1959. 5. Sloane, R. B.; Habib, A., and Batt, U. E.: Canad. M.A.J. *80*:540, 1959. 6. Straker, M.: Canad. M.A.J. *80*:546, 1959. 7. Strauss, H.: New York J. Med. *59*:2906, 1959.

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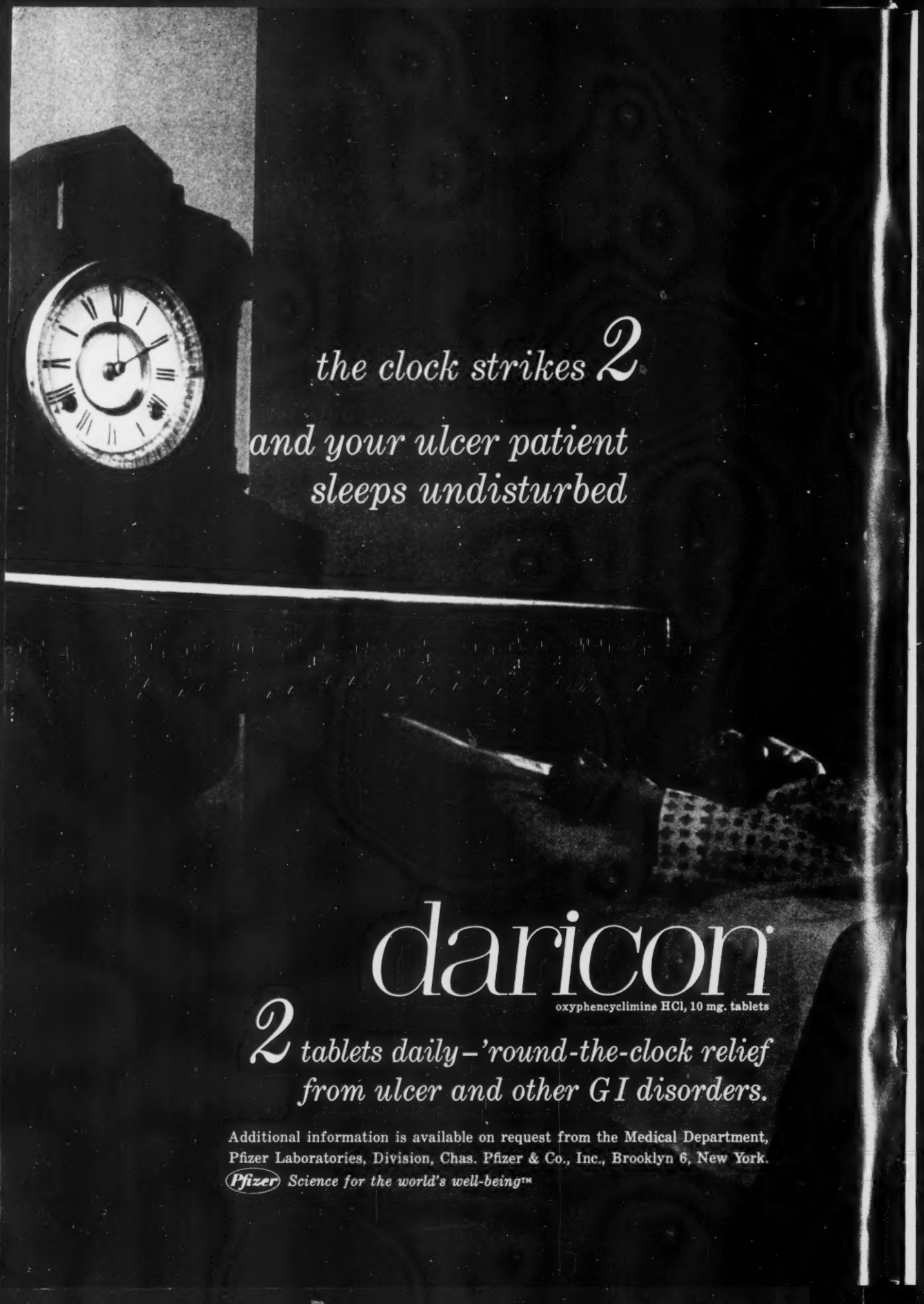
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from ulcer and other GI disorders.
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no irritating crystals[1] · uniform concentration in each drop[2]

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1. Lippmann, O.: Arch. Ophth. **57**:339, March 1957.
2. Gordon, D.M.: Am. J. Ophth. **46**:740, November 1958.

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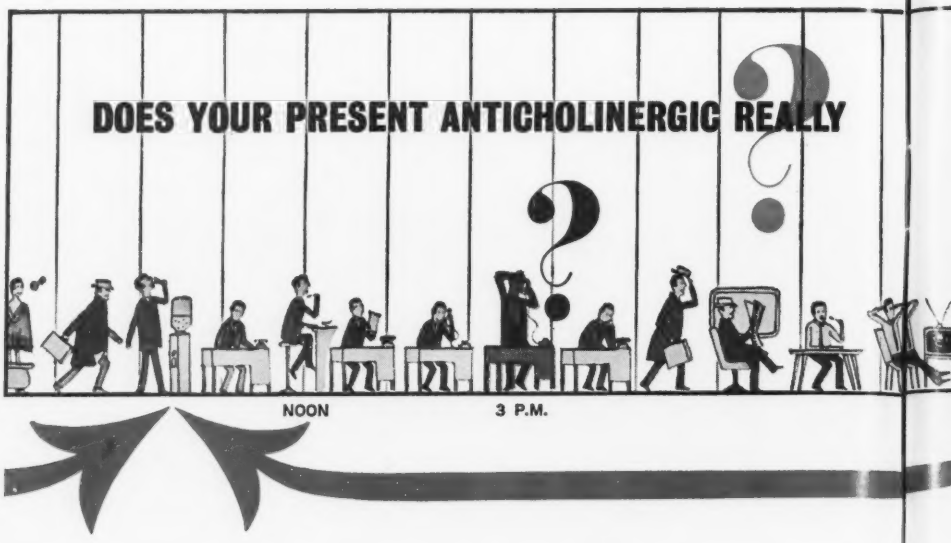


The test—you might say the acid test—of an anticholinergic is simple: will it protect your patient from hyperacidity around the clock, **even while he sleeps.** The weakness of t.i.d. or q.i.d. preparations is well recognized; but even some "b.i.d." encapsulations may be unreliable. McHardy, for instance, found a "widely variable duration of action, definitely less than that anticipated" in the "sustained," "delayed," and "gradual release" anticholinergics he studied.[1]

COMPARE THE DATA ON ENARAX... the new combination of an **inherently** long-acting anticholinergic (oxyphencyclimine) and Atarax, the non-secretory tranquilizer. Note the effectiveness of oxyphencyclimine:

OBSERVE THE OXYPHENCYCLIMINE REPORTS...

McHardy: "[Oxyphencyclimine] has proved to be an excellent sustained-action anticholinergic in our study of this agent over a period of eighteen months."[1]

Kemp: "...for the majority of patients, one tablet every 12 hours provided adequate control. This characteristic long action...may constitute an advantage of this drug as compared to coated 'long-acting' preparations of other compounds."[2]

Add Atarax to this 12-hour anticholinergic. The resulting combination—ENARAX—now gives relief from emotional stress, in addition to a reduction of spasm and acid. Atarax does not stimulate gastric secretion. No serious adverse clinical reaction has ever been documented with Atarax.

LOOK AT THE RESULTS WITH ENARAX[4,5]:

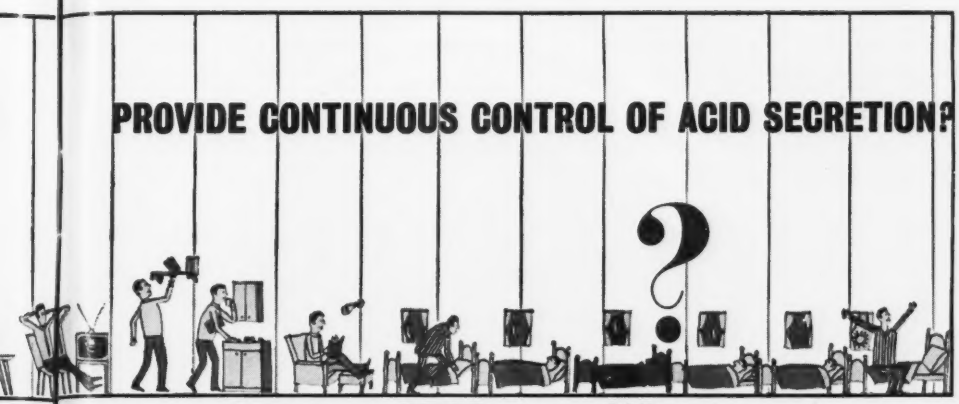
Does the medication you now prescribe assure you of all these benefits? If not, why not put your next patient with peptic ulcer or G.I. dysfunction on therapy that **does.**

ENARAX®

(oxyphencyclimine plus ATARAX®)

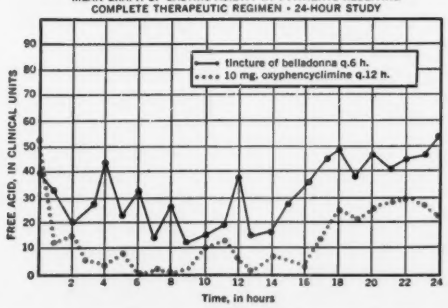
A SENTRY FOR THE G.I. TRACT

PROVIDE CONTINUOUS CONTROL OF ACID SECRETION?



"Prolonged periods of achlorhydria" after 10 mg. oxyphencyclimine q. 12 h.[3]

MEAN GRAPH OF GASTRIC ACIDITY IN 4 PATIENTS RECEIVING COMPLETE THERAPEUTIC REGIMEN • 24-HOUR STUDY



Clinical Diagnosis: Peptic Ulcer—Gastritis—Gastroenteritis—Colitis—Functional Bowel Syndrome—Duodenitis—Hiatus Hernia (symptomatic)—Irritable Bowel Syndrome—Pylorospasm—Cardiospasm—Biliary Tract Dysfunctions—and Dysmenorrhea.

Clinical Results: Effective in over 92% of cases.

As for Safety: "Side reactions were uncommon, usually no more than dryness of the mouth...."[4]

Each ENARAX tablet contains:

Oxyphencyclimine HCl ..... 10 mg.
Hydroxyzine (ATARAX®) ..... 25 mg.

Dosage: One-half to one tablet twice daily—preferably in the morning and before retiring. The maintenance dose should be adjusted according to therapeutic response. Use with caution in patients with prostatic hypertrophy and with ophthalmological supervision only in glaucoma.

Supplied: In bottles of 60 black-and-white scored tablets.

References: 1. McHardy, G., et al.: J. Louisiana M. Soc. 111:290 (Aug.) 1959. 2. Steigmann, F.: Study conducted at Cook County Hospital, Chicago, Illinois, in press. 3. Kemp, J. A.: Antibiotic Med. & Clin. Therapy 6:534 (Sept.) 1959. 4. Leming, B. H., Jr.: Clin. Med. 6:423 (Mar.) 1959. 5. Data in Roerig Medical Department files.

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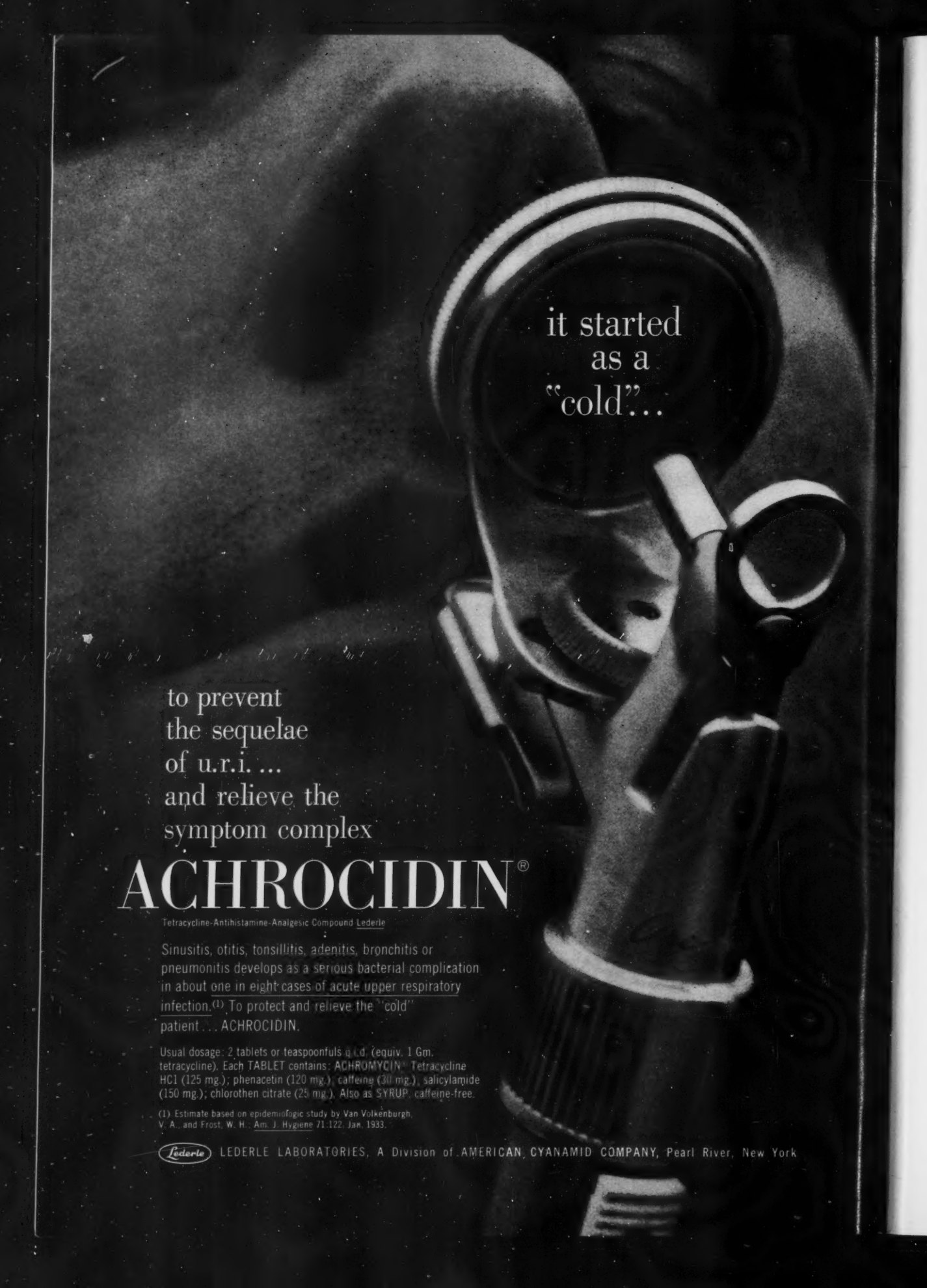
it started
as a
"cold"...
to prevent
the sequelae
of u.r.i. ...
and relieve the
symptom complex
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Tetracycline-Antihistamine-Analgesic Compound Lederle
Sinusitis, otitis, tonsillitis, adenitis, bronchitis or pneumonitis develops as a serious bacterial complication in about one in eight cases of acute upper respiratory infection.(1) To protect and relieve the "cold" patient... ACHROCIDIN.
Usual dosage: 2 tablets or teaspoonfuls q.i.d. (equiv. 1 Gm. tetracycline). Each TABLET contains: ACHROMYCIN® Tetracycline HCl (125 mg.); phenacetin (120 mg.), caffeine (30 mg.), salicylamide (150 mg.); chlorothen citrate (25 mg.). Also as SYRUP, caffeine-free.
(1) Estimate based on epidemiologic study by Van Volkenburgh, V. A., and Frost, W. H.: Am. J. Hygiene 71:122, Jan. 1933.
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Just one prescription for Engran Term-Pak
SQUIBB VITAMIN-MINERAL SUPPLEMENT *(270 tablets)*
calling for just one tablet per day will carry her through term to the six-week postpartum check-up. Thus, you help to assure a nutritionally perfect pregnancy, while providing the convenience and economy of the re-usable Term-Pak.

Engran is also available in bottles of 100 tablets.

SQUIBB *Squibb Quality—The Priceless Ingredient*

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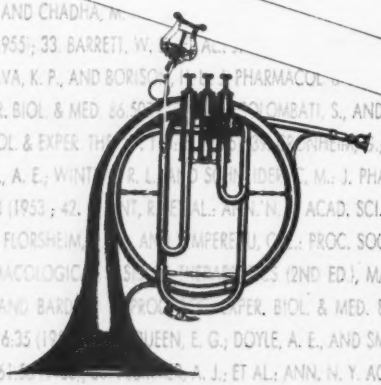

Only time and clinical acceptance truly define whether a drug is safe and effective. Of the many Rauwolfia compounds, there is one alkaloidal fraction capable of producing antihypertensive benefits with minimal side effects, purified alseroxylon complex (RAUTENSIN®).[1-6] This compound is less likely to cause such side effects as mental depression, lethargy, listlessness, and drowsiness consistently reported with reserpine.

IN MILD HYPERTENSION

RAUTENSIN®

(Tablets containing 2 mg. purified alseroxylon complex)

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RAUVERA®

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Rautensin bibliography: 1. WRIGHT, W. T., JR.; POKORY, C., AND FOSTER, T.: AM. PRACT. & DIGEST. TREAT. 7:1992, 1956. 2. SUCKLE, E.: GERIATRICS 11:509, 1956. 3. FINCH, W. J.: J. OKLAHOMA M.A. 50:259, 1957. 4. TERMAN, L. A.: ILLINOIS M. J. 3:67, 1957. 5. GIFFORD, R. W.: J. ARKANSAS M. SOC. 53:31, 1958. 6. FORD, R. V., AND MOYER, J. H.: POSTGRAD. MED. 23-41, 1958.

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when self-medication has delayed medical attention...

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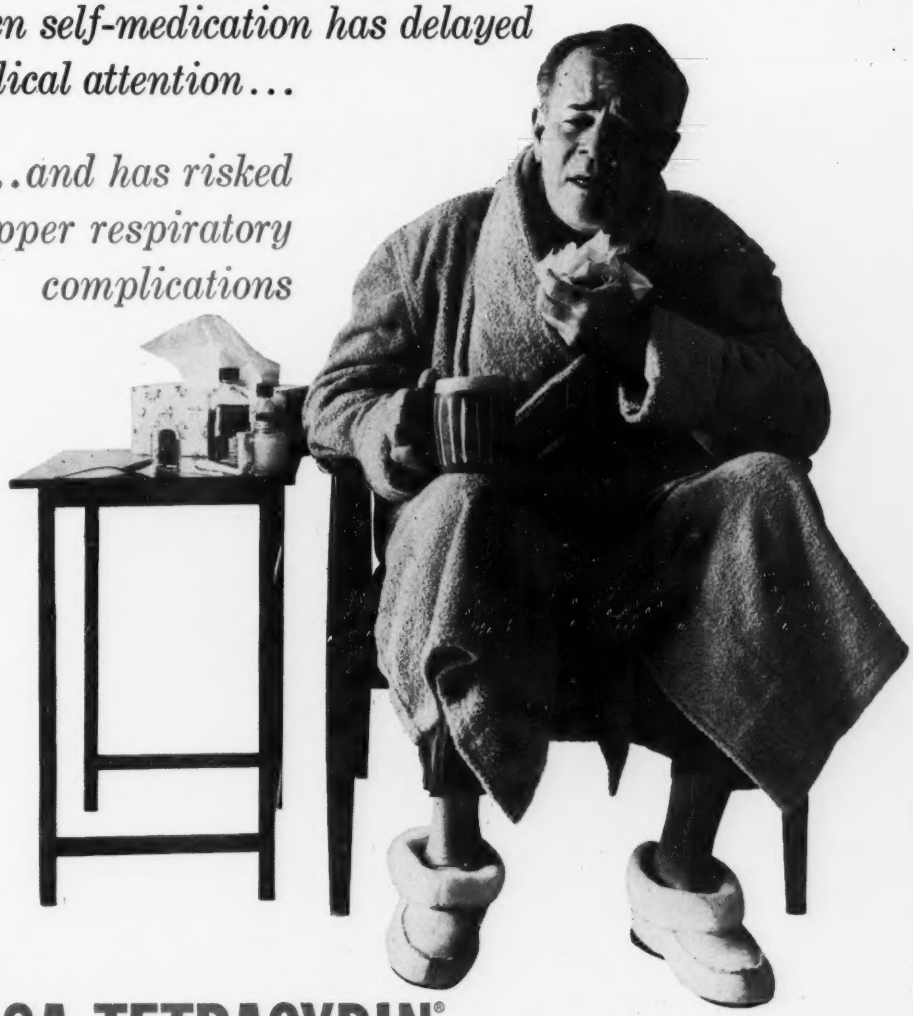

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Cosa-Tetracyn® — analgesic — antihistamine compound

act quickly to

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- *alleviate cold symptoms*

each capsule contains:

Cosa-Tetracyn	125 mg.
phenacetin	120 mg.
caffeine	30 mg.
salicylamide	150 mg.
buclizine HCl	15 mg.

average adult dose: 2 capsules q. i. d.

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Squibb Alpha-Phenoxyethyl Penicillin Potassium

new chemically improved penicillin which provides the highest blood levels that are obtainable with oral penicillin therapy

As a pioneer and leader in penicillin therapy for more than a decade, Squibb is pleased to make Chemipen, a new chemically improved oral penicillin, available for clinical use.

With Chemipen it becomes possible as well as convenient for the physician to achieve and maintain higher blood levels—with greater speed—than those produced with comparable therapeutic doses of potassium penicillin V. In fact, Chemipen is shown to have a 2:1 superiority in producing peak blood levels over potassium penicillin V.*

Extreme solubility may contribute to the higher blood levels that are so notable with Chemipen.* Equally notable is the remarkable resistance to acid decomposition (Chemipen is stable at 37°C. at pH 2 to pH 3), which in turn makes possible the convenience of oral treatment.

And the economy for your patients will be of particular interest—Chemipen costs no more than comparable penicillin V preparations.

Dosage: Doses of 125 mg. (200,000 u.) or 250 mg. (400,000 u.), t.i.d., depending on the severity of the infection. The usual precautions must be carefully observed with Chemipen, as with all penicillins. Detailed information is available on request from the Professional Service Department.

Supply: Chemipen Tablets of 125 mg. (200,000 u.) and 250 mg. (400,000 u.), bottles of 24 tablets. Chemipen Syrup (cherry-mint flavored, nonalcoholic), 125 mg. per 5 cc., 60 cc. bottles.

*Knudsen, E. T., and Rolinson, G. N.: Lancet 2:1105 (Dec. 19) 1959.

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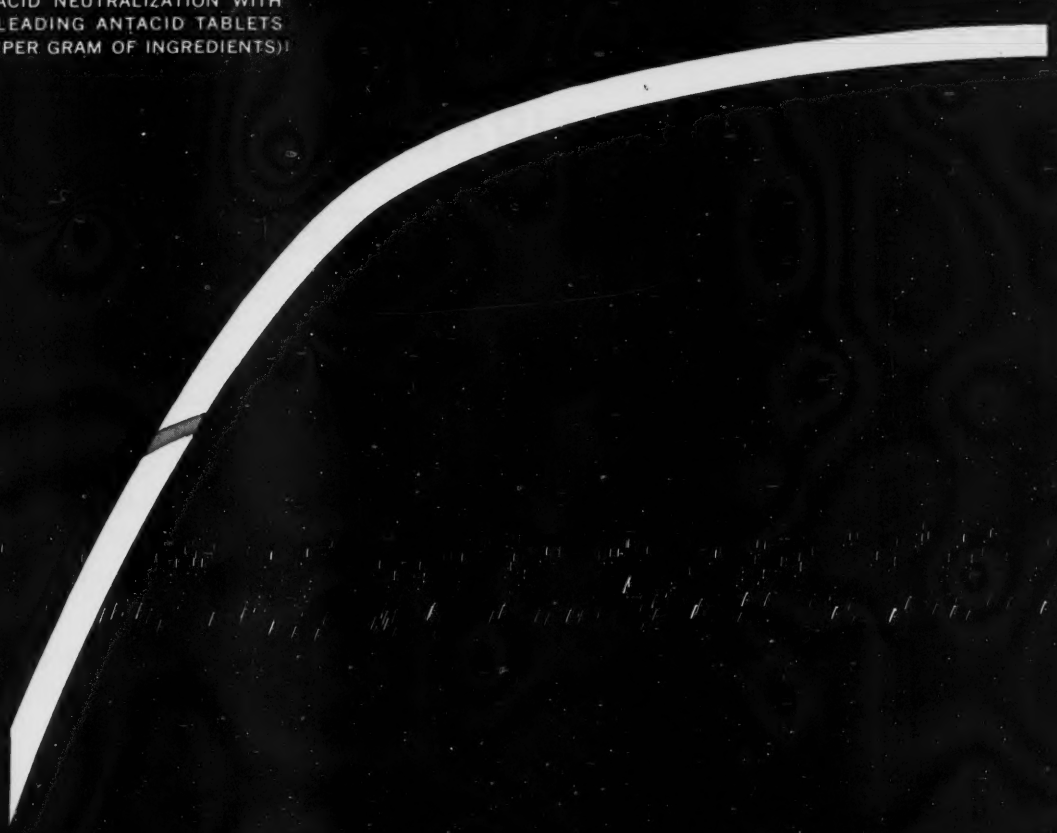
Squibb Quality—the Priceless Ingredient

More gastric acid neutralized faster...with new



GREATLY HEIGHTENED REACTIVITY to acid characterizes the action of New Creamalin Antacid Tablets.[1,2] They act faster and longer than other leading tablets and neutralize considerably more acid.[1] These tablets provide virtually the same effects as a liquid[2] with the convenience of a tablet. New Creamalin tablets give faster, greater and more prolonged relief.

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EACH NEW CREAMALIN ANTACID TABLET contains 320 mg. of specially processed, highly reactive, short polymer dried aluminum hydroxide gel (stabilized with hexitol), with 75 mg. of magnesium hydroxide.

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How Supplied: Bottles of 50, 100, 200 and 1000.

1. Hinkel, E. T., Jr.; Fisher, M. P., and Tainter, M. L.: *J. Am. Pharm. A. (Scient. Ed.)* 48:380, July, 1959. 2. Hinkel, E. T., Jr.; Fisher, M. P., and Tainter, M. L.: *J. Am. Pharm. A. (Scient. Ed.)* 48:384, July, 1959.

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Others may imitate, but none can duplicate the quality of Kent.

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control at every stage of anticoagulant therapy rapidity of induction and recovery time predictability of initial and maintenance dosages stability of therapeutic prothrombin levels during maintenance therapy reversibility of anticoagulant effect with vitamin K_1 preparations... rapid return to therapeutic levels on remedication

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Single daily dose convenience

Packaging—MIRADON Tablets, 50 mg., bottle of 100.

For complete information on indications, dosage, precautions, and contraindications consult the Schering Statement of Directions.

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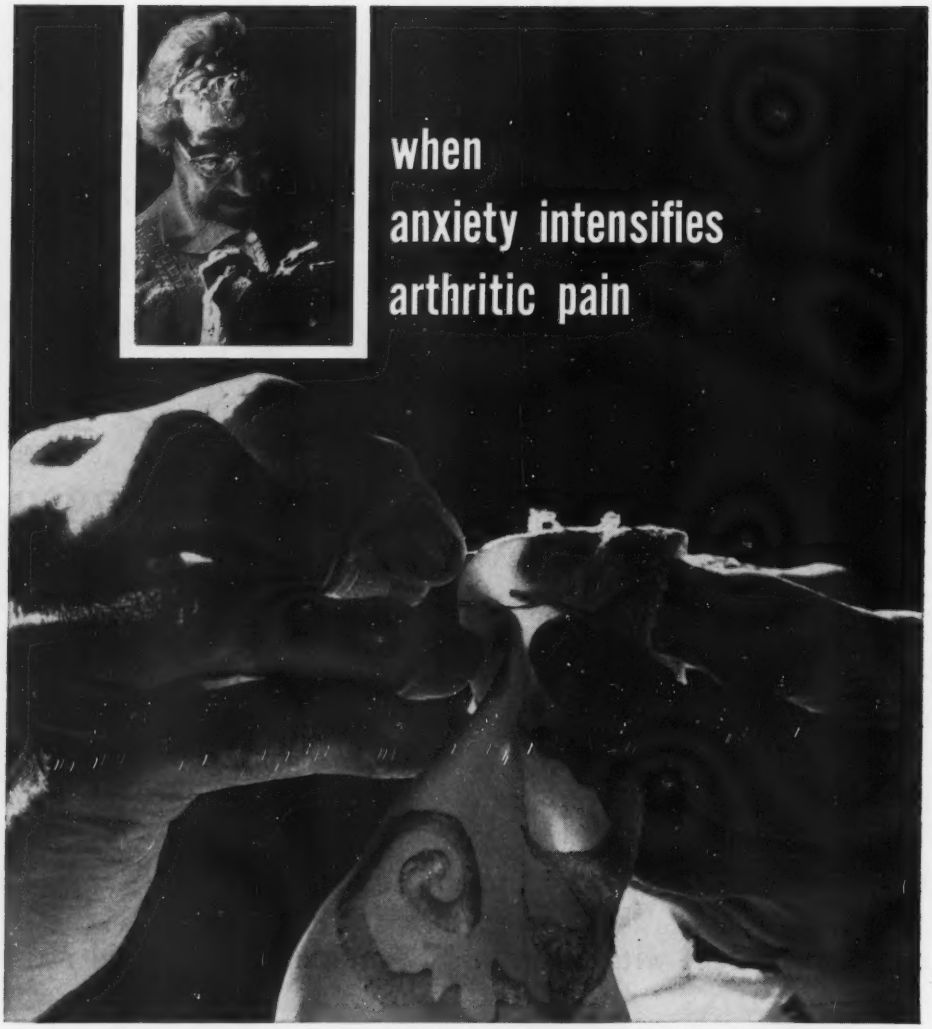

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Effective analgesia *plus* safe relief of mild anxiety helps combat the pain-anxiety spiral. In Darvo-Tran, the tranquilizing properties of Ultran® are added to the established analgesic effects of Darvon® and the anti-inflammatory benefits of A.S.A.®. Clinical and pharmacologic studies have shown that when pain is accompanied by anxiety, the addition of Ultran *enhances* and *prolongs* the analgesic effects of Darvon.

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Ultran	150 mg.	TO RELIEVE ANXIETY

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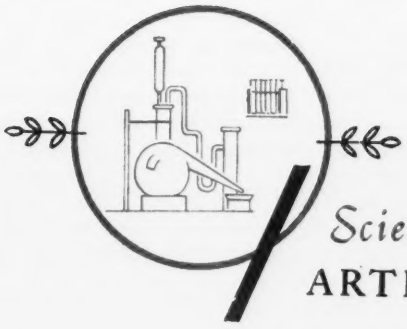

Scientific
ARTICLES

1959 and Forward

A Report from the Dean of the University of Kansas Medical Center

IT IS A PRIVILEGE once more to write a prefatory statement for the University of Kansas Medical Center issue of the JOURNAL OF THE KANSAS MEDICAL SOCIETY. The report of the past year and of the present one continues to be one of growth and progress. The salient features of that story follow.

Personnel. From the standpoint of faculty changes, there were several that bear mention here.

On *June 30, 1959, Dr. Leroy A. Calkins* reached the point of statutory retirement from his position as chairman of the Department of Gynecology and Obstetrics. Dr. Calkins had been chairman of the department since 1929 and in that position had the longest tenure of any departmental chairman in the School of Medicine. The growth of the department over the period of 30 years was entirely a credit to Dr. Calkins.

His retirement as chairman, of course, does not mean his retirement from the active faculty of the School of Medicine. He will continue as professor of Gynecology and Obstetrics as a teacher, investigator, and clinician.

On *July 1, 1959,* the chairmanship of the Department of Gynecology and Obstetrics was assumed by *Dr. Kermit Krantz.* Dr. Krantz came to the school from the University of Arkansas School of Medicine where he had been an assistant professor of Gynecology and Obstetrics since 1955. He is a graduate of Northwestern University School of Medicine. His graduate training in obstetrics and gynecology was obtained at Cornell University and the University of Vermont. Dr. Krantz, whom many of you have already met through your local societies and through his appearance on our circuit courses, brings to the department dynamic leadership.

On *September 1, 1959, Dr. Robert E. Stowell* resigned as chairman of the Department of Pathology and Oncology to take over the position of scientific director of the Armed Forces Institute of Pathology. Dr. Stowell had been a member of the faculty of the School of Medicine since 1948. Under his leadership, the Department of Pathology had experienced tremendous growth. The volume of research carried on in the department was a credit to the Medical Center; the distinguished faculty that he brought to this Medical School was a source of great pride to all of us. Several of his young men have gone on to become chairman of departments in other schools of medicine. Dr. Stowell's leaving, although regretted deeply, is also a source of pride to the Medical Center in that the position he has now accepted is looked upon as the most prominent position in pathology in this country, if not in the world.

On *November 1, 1959, Dr. Vernon E. Wilson's* resignation as associate dean of the School of Medicine became effective. On that date Dr. Wilson assumed his new responsibilities as dean of the University of Missouri School of Medicine and director of the University of Missouri Medical Center. Dr. Wilson had been a member of this faculty since 1953 and associate dean of the medical school since 1957. I believe there are few of you who have not come to know Vernon intimately. All of you must know how deeply we will miss him. The fact that he has gone to greater responsibility once more makes us prideful.

On *November 15, 1959, Dr. E. Grey Dimond,* chairman of our Department of Internal Medicine since 1952, announced his resignation, effective June 30 of this year. At that time Dr. Dimond will move his research and teaching activities to the Scripps Research Foundation in La Jolla, California. Little that can be said here would add to the knowledge that you already have of Dr. Dimond's dynamic leadership of the Department of Medicine, of his crucial role in the postgraduate activities of that department and particularly his own area of cardiology. His presence will be missed by all of us.

On *December 1, 1959, Dr. Robert P. Hudson* assumed his duties as assistant dean of the School of Medicine in charge of student affairs. Dr. Hudson is a graduate of this School of Medicine with the class of 1952. He has been a member of this faculty since 1958. Dr. Hudson's attributes are very much like those of Dr. Wilson, and we look forward to his continued growth in this position. We hope that all of you will soon become well acquainted with him.

On *January 1, 1960, Dr. John R. Carter* joined the faculty of the School of Medicine as chairman of the Department of Pathology and Oncology. Dr. Carter comes to us from the School of Medicine of the State University of Iowa where he had been a member of the faculty for 11 years. Dr. Carter is a graduate of the University of Rochester School of Medicine. His graduate training in pathology was received at the State University of Iowa. Dr. Carter has been a key member of the faculty at Iowa for a considerable number of years. We look forward with pleasant anticipation to his efforts here with us.

A committee of the faculty is now actively at work seeking a successor to Dr. Dimond. As soon as a successor has been found, a suitable announcement will be made to the Kansas Medical Society.

Facilities. Since a report was last given to you in these pages, the remodeling of several floors in the Hixon Building has come nearly to completion. As many projects go, this one has taken longer than we had anticipated, but we are looking forward to moving into the remodeled areas within the next month or six weeks.

On the corner of 39th and Cambridge, there is now under construction a half million dollar building designed for the use of the Communicable Disease Center of the United States Public Health Service. This building is being constructed by the Kansas University Endowment Association under a lease agreement with the General Services Administration of the Federal Government. When it is completed, the quonset-type building presently housing the C.D.C. Laboratories, under the direction of Dr. Furcolow, will be vacated.

Architectural plans are now nearly complete for the construction of an addition to Wahl Hall which will make possible the ultimate consolidation of the School of Medicine on this campus in Kansas City.

At the 1959 session of the Kansas Legislature, the sum of $1,000,000 was made available to match federal funds, making this building a reality. It is our hope that bids will be taken on this project in March and that construction will be enabled to begin in June.

Budget. This progress report is being written at a time when the Legislature is in session. Up to this moment, the appropriation measure for the Medical Center has passed the Senate and is now before the House for its consideration. I am happy to report that the Legislature has provided the necessary appropriations to meet our entire request for the forthcoming fiscal year.

Conclusion. It is once more a source of great satisfaction for me to report that the relationships between School and Society continue at the very highest level. This year we felt constrained to call upon the Society for assistance in our budgetary problems. Nothing could have pleased us more than the magnificent spirit with which the Society came to our support, immediately, unanimously, and wholeheartedly, and for this understanding support and encouragement, we are extremely grateful.

W. Clarke Wescoe, M.D., Dean

The University of Kansas School of Medicine

Postgraduate Medicine

A Report of the Department of Postgraduate Medical Education

MAHLON DELP, M.D.; JESSE D. RISING, M.D.; *and* WILLIAM D. NELLIGAN, B.S., *Kansas City*

EACH YEAR THE DEPARTMENT of Postgraduate Medical Education prepares, primarily for the administration of the University and the School of Medicine, an annual report. This information has limited circulation, and consequently only a few members of our student body, the physicians of Kansas, have a current view of the department's total activity. Toward this group we have a feeling of real gratitude and responsibility, and to them we direct this report.

Forty-Fifth Year of Continuation of Medical Education

The School of Medicine can feel a justifiable degree of satisfaction in this, its 45th year of continuation education in medicine, and therefore presents this review of the past year's work. Included with the text of this report are charts depicting some of the more important information.

No change in administrative structure or function has been made in the past year. We have leaned more heavily upon the Executive Faculty of the School of Medicine than in the past, presenting to them many of our problems having implications of policy for both their information and advice. We can safely say that this medical school faculty has a better grasp of basic concepts, objectives and methods in this phase of medical education than does any other similar faculty in the country. Our Postgraduate Advisory Committee likewise represents a superbly oriented, responsible and thoughtful group of physicians in Kansas who are extremely helpful in guiding this program in which they have a heavy intellectual investment. We are firmly convinced that ours is a sound administrative structure infinitely more logical in form than the so-called postgraduate schools with their sometimes-functioning faculties and paper organizations. Our school is one solid group engaged in the effort of medical and health education with common objectives and minimum distractions.

Thirty-Nine Courses Offered

The academic year 1958-59 was finished with the program, "What's New in Orthopedics," completing an array of 39 courses not including the circuit sessions at 10 centers and omitting the repetitions of the correspondence courses in electrocardiography and hematology. This represents 11 more courses than were given the previous year. The increased number of offerings is not in itself a real feat or accomplishment. We do, however, wish to comment upon individual programs. The Department of Nursing Education has made remarkable progress this year with a series of new projects including a "Nursing Workshop" at Garden City. Some of this work simulates graduate education, but if our department can be of service in furthering such it should. The success of these exercises in nursing education has been so encouraging as to open up a wide field untouched in our community of responsibility.

A course in temporal bone surgery given by the Department of Otorhinolaryngology to a small group of physicians was an outstanding venture. "The Ophthalmoscope: Its Use in Medicine" employed new teaching methods with gratifying results. Similar remarks can be made of the courses, "Glaucoma" and "What's New in Orthopedics." The latter was an initiatory project and, judging from the spontaneous approval of the small group attending, was an excellent teaching contrivance. "Cardiac Auscultation" was, by request, repeated during the year by the cardiovascular staff. A small group; close personal instruction; and the use of phonocardiograms, sound equipment, electronic stethoscope jacks, recorded tapes, and patients formed the design most certain to teach and train.

Short Courses Increase

Larger enrollment short courses ("symposia") such as those in "Obstetrics," "Internal Medicine," "Pediatrics," and "Surgery" continued popular and drew large numbers of students from all parts of the country. A skillful guest moderator for all sessions of the obstetrics program proved to be one of the most profitable of recent innovations in various teaching techniques. The surgery program, scheduled in May rather than in January, had its greatest enrollment and received its most laudatory responses to questionnaires. A series of short teaching movies pro-

From the Department of Postgraduate Medical Education, University of Kansas School of Medicine.

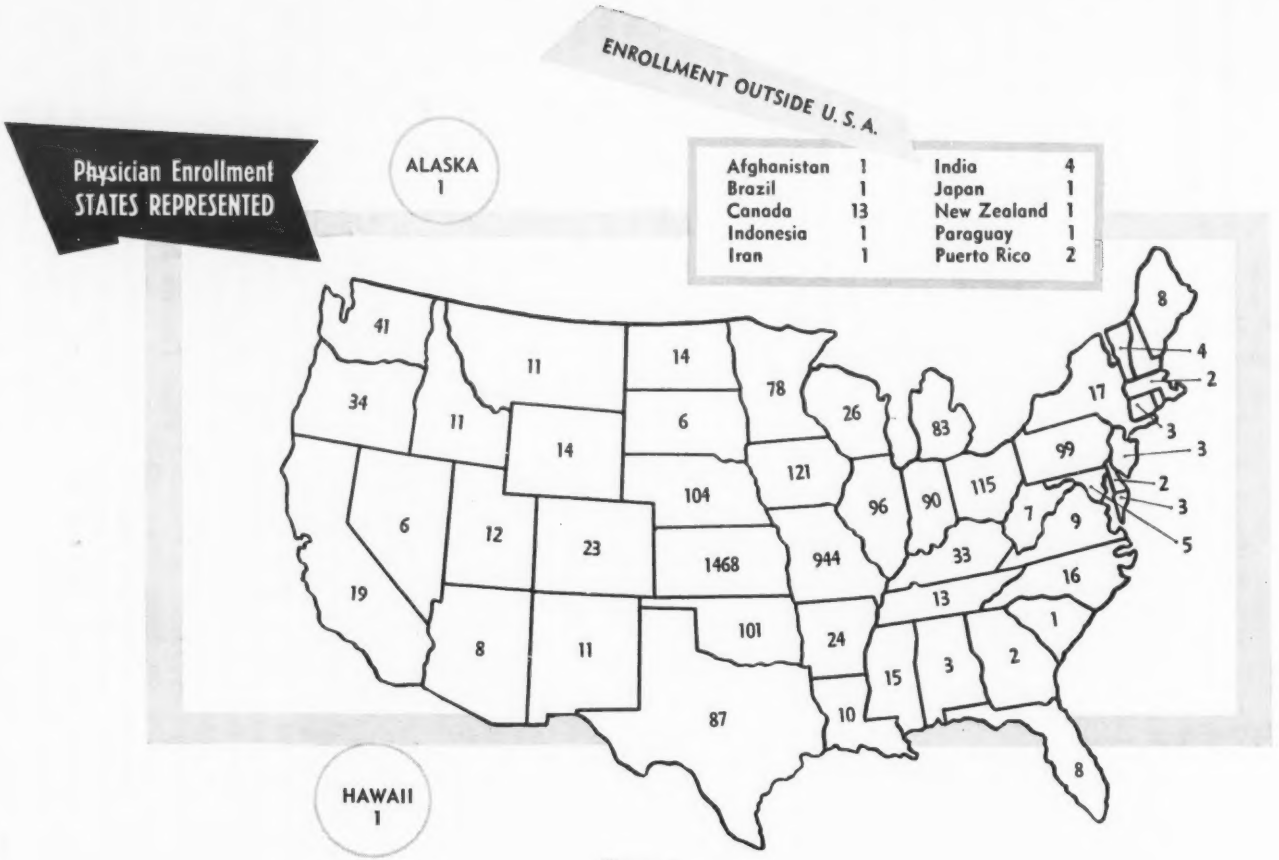
Physician Enrollment
STATES REPRESENTED
ALASKA
1
HAWAII
1
ENROLLMENT OUTSIDE U. S. A.
Afghanistan 1
Brazil 1
Canada 13
Indonesia 1
Iran 1
India 4
Japan 1
New Zealand 1
Paraguay 1
Puerto Rico 2
41
34
11
11
14
14
6
104
78
121
26
96
83
90
99
115
17
7
9
8
4
2
3
3
2
3
5
6
12
23
1468
944
33
13
16
1
19
8
11
101
24
15
3
2
87
10
8

Figure 1

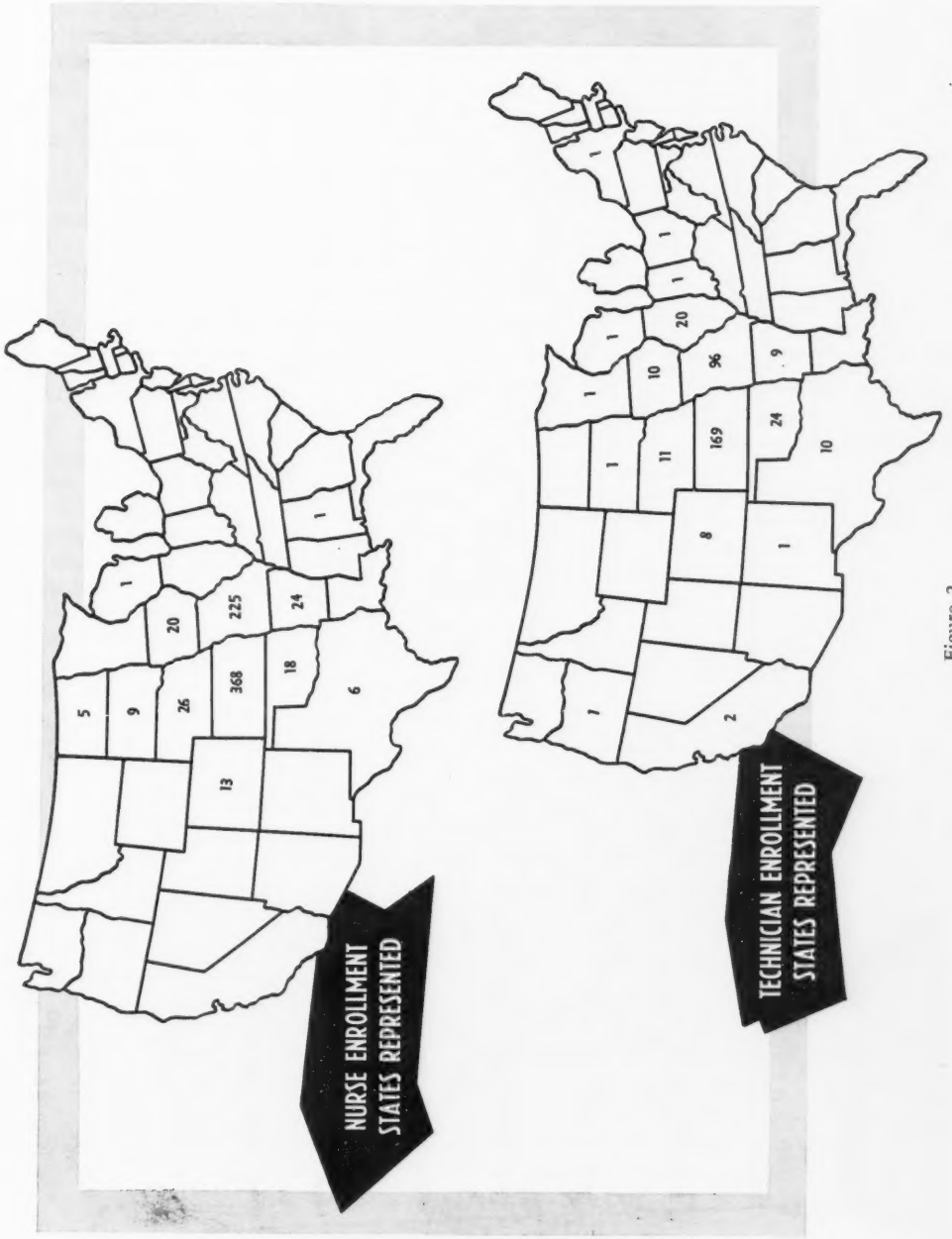
NURSE ENROLLMENT
STATES REPRESENTED
5
9
26
368
13
18
6
20
225
24
1
1
TECHNICIAN ENROLLMENT
STATES REPRESENTED
1
2
1
8
1
1
11
169
24
10
1
10
96
9
20
1
1
1

Figure 2

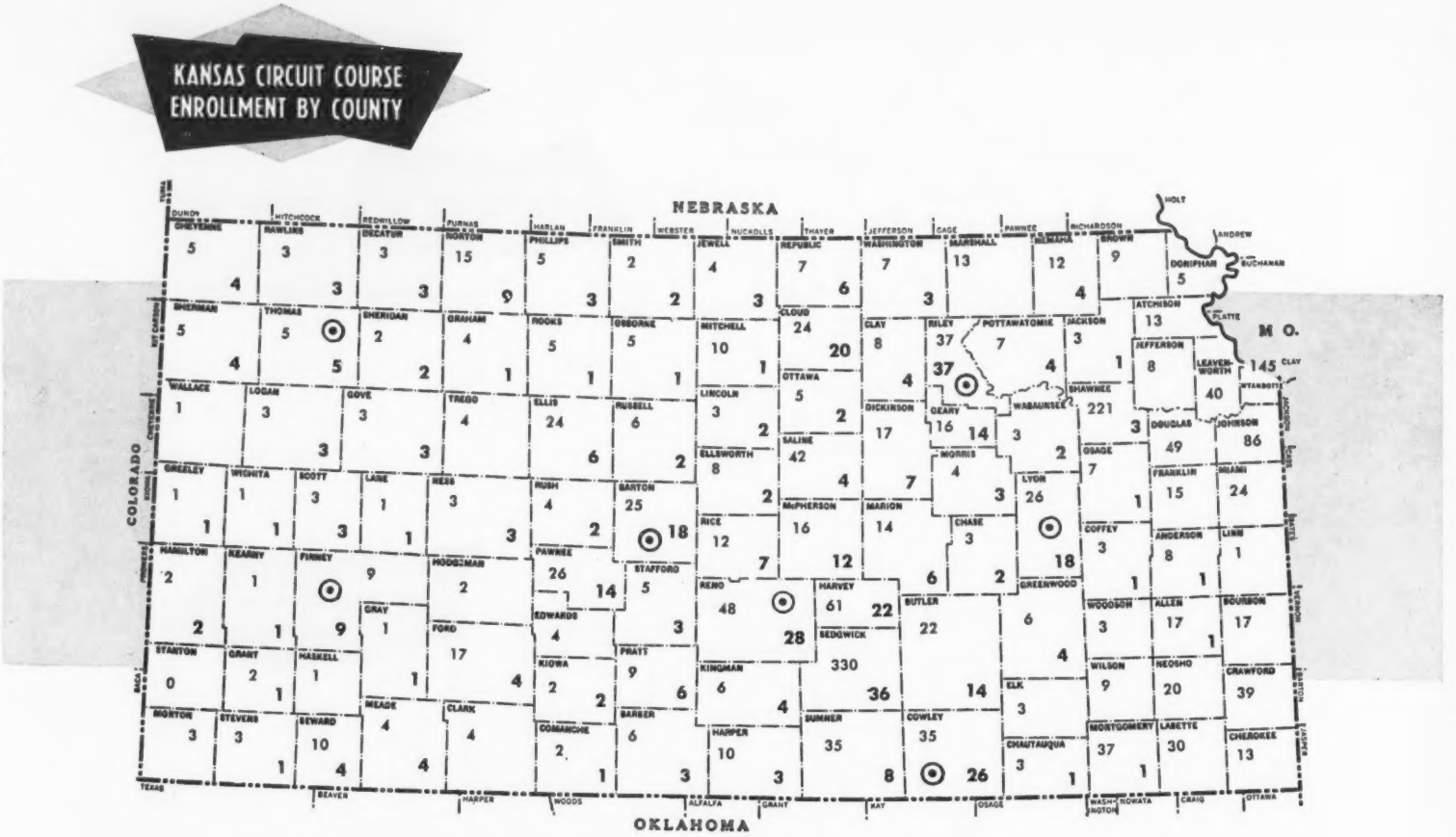
KANSAS CIRCUIT COURSE
ENROLLMENT BY COUNTY
NEBRASKA
COLORADO
OKLAHOMA
MO.
Circuit Center
00 Total Number Physicians in County
00 Total Number Physicians in attendance at one or more Circuit Course Sessions (nine enrollments from Oklahoma physicians)

Figure 3

duced in our own institution were successfully used in this program.

The short courses or "symposia" present some problems as teaching projects. The groups are frequently large and much teaching follows the didactic method; but several comments are pertinent: Criticism of similar methods used in undergraduate medical school teaching are far from appropriate here, and the "symposia" are distinctly superior to the ordinary medical meeting. With ingenuity in teaching plans and methods a large group can be moulded into a participating student body simulating the intimacy usually accomplished more easily with a small group. Our faculty, by experience, is expert in this. The nursing group this year divided groups of 75 and 100 into several small discussion groups, and continued instructions for four or five days in such pattern.

Single Subject Presentations

We are enthusiastic about single-subject presentations such as the program on "Glaucoma." Of course, we reiterate the superiority of the "clinical traineeship" over all other forms of postgraduate education and training; but, if basic principles of postgraduate medical education are kept in view, all methods have value and must be appropriately exploited if we are to attain our broad objectives.

Results of an intensive study of the nature of medical practice, carried on by our own "preceptors" in Kansas, were published under the title of "General Practice in Kansas."[1] The importance we attach to introspective study of our program of continuing medical education is well known. There are few if any real sources of accumulated information in this field, and our program by virtue of age and experience is obligated to record these. Collection and analysis of data will continue indefinitely as a regular departmental function in research.

TABLE I

PHYSICIAN ENROLLMENT FREQUENCY

No. of Physicians	*No. of Courses Attended*	*Total No. of Physician Enrollments*
2192	1	2192
486	2	972
139	3	417
30	4	120
12	5	60
4	6	24
3	7	21
..	8	..
..	9	..
2	10	20
..	11	..
1	12	12
2869		3838

TABLE II

KANSAS CIRCUIT COURSE ENROLLMENT BY CENTER

Circuit Centers	*Physicians in Area*	*Number Attended*	*Percentage Attended*
Manhattan	120	76	63
Hutchinson	170	90	53
Arkansas City	96	56	58
Emporia	53	27	51
Concordia	104	43	41
Colby	52	40	77
Garden City	76	39	51
Great Bend	120	55	46
Total	791	426	53.9

An even larger number of guest faculty was used this year than previously, chiefly because more programs were produced. Other organizations interested in postgraduate medical education do not understand our liberal use of distinguished guest faculty. The answer is simple: by tradition our student body expects it, and heartily endorses the practice; and because of careful selection these teachers enhance, inspire the students, and adorn the instructional atmosphere. We shall continue this custom.

Our own medical faculty members have long accepted their responsibilities for postgraduate teaching and do it in the same manner as they do the teaching of medical students, nurses, technologists, graduate students, internes, and residents. All of the circuit-type teaching is done by our own faculty; a high percentage of the basic science instruction is given by our own group; and virtually all of the small-group instruction in any program is given by our staff. Naturally, the "clinical traineeships" are carried on purely by our own teachers.

Enrollment Figures Tell of Popularity

It is readily admitted that enrollment figures are relatively unimportant, and should in no way be construed as indicating the effectiveness or quality of the program. They can, however, safely be said to indicate the popularity of the program and its convincing promotion. During the 1958-59 school year 3,838 physicians were enrolled. This is an increase of nearly 500 over the preceding year. (We had actually anticipated a decrease in total registration for the year.) It should be understood that 610 of

(Continued on page 121)

Ventilation During Anesthesia

The Problem of Maintaining Adequate Respiration During Anesthesia

JOHN I. DAVIES, M.D., F.R.C.P.(C), *Kansas City*

THE IMPORTANCE OF ADEQUATE respiration in maintaining consciousness and life was well recognized in antiquity, so it is not surprising that when general anesthetics were first administered over 100 years ago considerable attention was paid to respiratory movements. John Snow described changes in the respiratory pattern during various depths of anesthesia and recorded a number of deaths during anesthesia in which respiratory obstruction and depression were contributory factors.

The Good Old Days

During the 1930's before the widespread popularity of cyclopropane, intravenous barbiturates, and the introduction of muscle relaxants, the usual general anesthetic techniques were either ether, or chloroform/ether mixtures by open drop methods, or "Gas, Oxygen, Ether" by some machine. Some anesthesiologists still refer to this period as "the good old days" and it was then thought that patients did not experience particular difficulties if:

1. A clear airway was maintained.
2. Oxygenation was adequate.
3. Anesthesia was lightened if respiration became seriously depressed.

However, these patients did not do as well as we were led to believe as one often saw post-operatively clinical signs of collapse or shock though it was unusual at that time to take B.P. readings. This state was attributed by anesthesiologists to surgical trauma and to the effects of deep prolonged anesthesia often demanded by the type of surgery; and by surgeons to poor administration of the anesthetic.

At the present time the problems associated with ventilation during anesthesia are receiving considerable attention. The reasons for this great interest include:

1. An increasing awareness of the importance of adequate ventilation.
2. The increasing frequency of thoracotomy and the problems associated with an open pneumothorax.
3. The common use of central respiratory depressant agents including cyclopropane, Fluothane, intravenous barbiturates, and analgesics such as Demerol.
4. The widespread use of muscle relaxants.
5. More operations are being performed on patients suffering from moderate and severe respiratory disorders.

It seems clear that as far as ventilation during anesthesia is concerned, the ideal can be summarized by the words of Claude Bernard "all the vital mechanisms, varied as they are, having only one object, that of preserving constant the conditions of life in the internal environment." This view was re-emphasized by Gordon who said, "we should undoubtedly be safer to think more in terms of maintaining a normal respiratory exchange in the individual patient than of trying to get rid of all possible carbon dioxide."[37]

Finally let us remember a quotation of Rowntree who said, "when our blood becomes as acid as triple distilled water, we will likely die in a coma; when it becomes as alkaline as ordinary tap water, we are likely to die in convulsions."

Ventilation Must Be Adequate

It is generally agreed that ventilation must be adequate:

1. To provide adequate oxygenation.
2. To ensure correct elimination of CO_2.
3. To avoid the deleterious effects of unphysiological respiratory movements and pressures on the cardiovascular system.

We are all familiar with the effects of oxygen lack which were described in detail by Haldane and later emphasized by Courville and many other authors. Clinically hypoxia is rarely a problem as oxygen enriched mixtures will compensate for minor degrees

Dr. Davies is the Assistant Professor of Surgery (Anesthesiology), University of Kansas School of Medicine, Kansas City, Kansas.

of obstruction or decreased tidal volume. Hypoxia may still be a potential danger if,

1. Large areas of the tracheobronchial tree are blocked by secretions.

2. Bronchial constriction occurs.

3. Large areas of lungs are compressed by retractors or packs, as during some thoracotomies.

4. Oxygen uptake is impaired by pulmonary disease.

However, an excess of oxygen given for even short periods may be harmful by causing vasoconstriction of cerebral vessels. This effect is well known in aviation circles, as the Oxygen Paradox[4] and has been utilized by some neurosurgeons in providing a relatively drier operative field.

Elimination of CO_2

The proper elimination of carbon dioxide is a far more difficult problem as complicating factors include:

1. Inadequate minute volume caused by

a. Centrally respiratory depressant agents.

b. Partial or complete paralysis of respiratory muscles.

c. Effects of certain postures and mechanical interference with respiratory movements.

Brownlee and Allbritten have shown that the actual work of breathing during general anesthesia may be increased many fold by factors which interfere with the movements of the chest wall, lung or diaphragm; by the general anesthesia itself; and by even the lateral position.

2. Ineffective soda-lime.

3. Defective or poorly designed apparatus.

4. An increase in dead space. This may be caused by mechanical means. It was shown by Folkow and Pappenheimer that the "parallel" or bronchiolar dead space may be increased by 150 per cent of its normal value by intratracheal pressures of 15-20 cm. of water. These pressures cause dilatation of bronchioles which stay dilated even when the pressures return to normal.

Severinghaus and Stupfel have shown that the anatomical dead space in man is increased about 30 per cent following 0.5 mgm. of atropine subcutaneously.

5. The use of semi-open methods of anesthesia. Elam and co-workers have shown that when this method is used, and inflow rates equal the patient's minute ventilation, the inspired gases contain between 1.2 and 4.2 per cent carbon dioxide, averaging 2.0 per cent.

The physiology of carbon dioxide and pulmonary ventilation is complicated but some points of interest are:

1. The tension of CO_2 in the arterial blood is the main factor in the control of normal respiration. This level is in equilibrium with the alveolar CO_2 concentration and normally equals a partial pressure of about 40 mm. Hg. The alveolar concentration is constant for a person for long periods of time and is about 5.4-5.6 per cent. If this percentage is increased by 0.23 per cent, ventilation is doubled if the respiratory center is active. Similarly reducing the level of CO_2 will lead to apnea.

2. The pCO_2 is mainly responsible in maintaining the pH of the blood at normal levels. If the normal ratio H_2CO_3/HCO_3 of 1/20 is disturbed a respiratory alkalosis or acidosis may occur particularly during anesthesia when the renal function is depressed. These changes would lead to important changes in the electrolyte balance. The Hamburger phenomenon or "Chloride shift" would lead to secondary changes in the intracellular levels of sodium, potassium, calcium, and magnesium.

The changes in blood pH and intracellular potassium are closely inter-related and greatly affect the distribution of intravenously administered barbiturates and muscle relaxants.

Barbiturates

Acidosis or lowering the blood pH tends to move barbiturates from the blood stream to inert tissue spaces, presumably extracellular. Raising the pH has the reverse effect.[9] This may explain why hypoventilated patients who have reacted to final skin suturing may a short time later appear deeply anesthetized.

Muscle Relaxants

Muscle relaxants do not usually have an effect on the central nervous system when given intravenously. However, it has been suggested that under conditions produced by respiratory acidosis, or intracellular potassium depletion, the blood brain barrier may be so altered that muscle relaxants will cross this barrier and produce a central effect.[10, 13] This central effect is characterized by:

1. An initial apparent resistance to the relaxant.

2. Loss of consciousness or prolonged unconsciousness.

3. Medullary depression affecting both the respiratory and cardiovascular systems.

4. Irreversability by neostigmine of competitive muscle relaxants, and may explain some cases of so-called neostigmine resistant curarization.

Cardiovascular System

Blood levels of CO_2 affect the cardiovascular system in a number of ways. Slight increases in CO_2 act as a central stimulant though peripherally a depressant effect (dilatation) occurs. Under these conditions blood pressure is raised, pulse rate is in-

creased, skin capillary blood flow is increased and veins are dilated. With higher concentrations of CO_2 collapse of the cardiovascular system may occur and in these circumstances death is attributed to a direct effect on the heart. Tenney has shown during experiments on dogs during diffusion ventilation that most of the cardiovascular effects of CO_2 retention are caused by a rapid rise in the titer of circulating adrenalin and nor-adrenalin. Burn has shown that an increase in circulating adrenalin is the main trigger for initiating Selye's stress-response reaction.

Electrocardiographically, CO_2 excess depresses the A-V conduction of the heart and complete block occurs at pH 7.0. The S-A node is also depressed and this tends to slow the heart rate and may precipitate arrhythmias.

On the other hand a deficiency of CO_2 causes a fall in blood pressure; cardiac diastole becomes less complete; the venous pressure falls; and the A-V conduction rate rises because of increased S-A nodal activity.

Van Bergen and co-workers have shown that some cases of postoperative and so-called "cyclopropane shock" are caused by the rapid postoperative lowering of CO_2 when patients breathe room air.

Cerebration

It was shown by Hickman in 1778 that CO_2 could be a narcotic. If conscious patients breathe concentrations of CO_2 as low as five per cent consciousness may be lost and 10 per cent is the upper limit of tolerance if consciousness is to be retained, and anesthesia of a sort occurs with 25-30 per cent CO_2. At 30 per cent convulsions occur and this has been utilized by some psychiatrists as an alternative to electro-convulsive therapy.[18] On the other hand Barach reported that cerebral efficiency decreases when the alveolar CO_2 is lowered 10 mm. Hg. below normal and that giddyness, disorientation and tetanic convulsions occur if the level falls below 23 mm. Hg.

Bohr Effect

The pCO_2 affects oxygen uptake and utilization by shifting the oxygen dissociation curve. Carryer as well as others believes that tissue hypoxia may result when the blood becomes sufficiently alkaline from hyperventilation.

Denstedt and McKearns have shown that either excess or lack of CO_2 may interfere with the transport of oxygen and also depress intracellular enzymatic activity, particularly those concerned with A T P. These effects may be secondary to changes in pH.

Miller and Brown and later Seevers have shown that animals can compensate fairly well to gradual changes in CO_2 concentration but that sudden changes produce the majority of the ill effects described.

As complicated as these effects may seem, during hypothermia, with the added possibility of metabolic tissue acidosis, the position is far more confusing, but of even greater importance.

Rappaport is among the few who currently believe that a primary visceral function of the lung exists as well as a purely physical function. This may explain in part the ability of Swann to resuscitate anoxic dogs with concentrations of oxygen as low as two per cent.

Ventilatory movements and alternative positive and negative intrathoracic pressure affects the cardiovascular system by aiding venous return to the heart. It is thought that these pressures can, by themselves, produce some coronary and pulmonary blood flow, even in the absence of an effective heart beat. Similarly increasing the mean intrathoracic pressure will, by impeding venous return, cause a lowering of cardiac output and fall in blood pressure.

Monitoring of Ventilation

It is thus apparent that it is the concern of every anesthesiologist to ensure that ventilation is adequate. In the investigation of these problems some aids include:

1. Oximeters
2. Estimation of blood pH, pO_2, and pCO_2
3. CO_2 analyzers such as
   a. The mass spectrograph
   b. Liston-Becker infra-red analyzer
   c. Draeger CO_2 analyzer (infra-red)
   d. Liquid color-change indicators (B.O.C., Ohio Chemical)
   e. Dewey & Almy quick acting chemical analyzer

Most are costly and not clinically practical. There is an undoubted need for a cheap reliable, efficient and rapid CO_2 analyzer. That of Dewey and Almy promises to fulfill these conditions—if $200.00 can be considered cheap.

4. Spirometers. In 1922 McKesson emphasized the need of measuring tidal and minute volume. Since then spirometry during anesthesia has been measured by various people including:
   a. Benson using a bellows type spirometer
   b. Lilley using a pneumotachygraph measuring the pressure differential across a Monel metal screen placed in the airway
   c. Moloney introduced a Venturi system measuring the pressure differential produced by a flow of gas in either direction
   d. Wright and Bennett introduced an anemometer of wind vane type to measure volumes directly which is suitable for inclusions in anesthetic circuits

TABLE I

(Modified from Fairley)
Canad. Anaes. Soc. J. 6:3, 225

	Primarily for OR	*Primarily for RT*	*Volume Constant*	*Pressure Constant*	*Gas Motive Force*	*Electric Motive Force*	*Circuit Type a*	*Circuit Type b*	*Circuit Type c*	*Patient-Triggered*	*Automatic*	*Switches Spontaneously*	*Negative Phase*	*Phase Variability*	*Automatic Bag Refill*	*Can Deliver Room Air*	*Alternative Bag*	*Alternative Concertina*	*Humidifier*	*Humidifier With Thermostat*	*Ve Easily Monitored*	*Warning Devices*		*CSA Approved*	*Built-in Manometer*	*Built-in Gas Meter*	*Built-in Suction*
																						Excessive Pressure	*Falling Pressure*				
Beaver		X	VL			X		X		X						X					X			X	X		
Bennett Resuscitator HR-5		X		X	X		X			X	X					X			X		X				X		
Bennett PR-1A		X		X	X		X			X	X	X							X						X		X
Bennett Assistor (BA-2)	X			X	X				X	X	X	X	X	X			X				X				X		
Bird Mark 7		X		X	X		X			X	X	X		X					X						X		
Bird A/C	XX		VL		X				X	X	X	X	X	X	X		X				X				X		
Blease P.3		X	VL			X		X		X	X	X	X	X		X		X			X		X	X	X		X
Blease Pulmoflators	X		VL			X			X		X		X	X		X		X	X		X		X	X	X		X
Emerson A/C	X				X				X	X	X	X	X	X		X	X				X				X		
Engstrom	X	X	VL			X		X			X		X	X		X	X			X	X				X	X	
Jefferson GH3	X		VL		X				X		X		X	X		X	X				X				X		
Jefferson A/C	X		VL		X				X	X	X	X	X	X		X	X				X				X		
Monaghan Ventalung		X		X	X		X			X	X								X						X		
Morch Surgical	X		VL		X				X		X		X	X				X			X				X		
Morch Piston		X	X			X		X			X					X		X	X		X			X			
Radcliff PNP		X		X		X		X			X		X			X				X	X	X			X	X	
Radcliff Portable PNP	X	X		X		X		X	X		X		X			X					X	X			X		
Radcliff IPP				X		X		X			X					X					X	X	X		X		
Stephenson CR U	X	X	VL		X			X	X		X		X	X		X		X			X						
Stephenson A/C	X	X	VL		X			X	X	X	X	X	X	X		X		X			X						
Van Bergen		X	X			X		X			X		X			X					X	X	X		X		

OR: operating room
RT: resuscitation therapy
VL: volume limited

Circuit type a. Intermittently opening reducing valve
b. Electrically driven piston or pneumatically driven piston
c. Compressible rebreathing bag in patient's circuit

e. Nunn introduced a method of spirometry applicable to all types of circuits

f. Roswell-Park ventimeter—another bellows type spirometer.

Radford Normogram

Radford has introduced his normograms, which consist of a series of graph and tables, from which a patient's minute volume can roughly be predicted. Allowance is being made for factors such as age, sex, size, and temperature.

Clinical signs, though said to be unreliable, cannot be lightly dismissed, and it seems to me a triumph that clinical anesthesiologists appear to maintain adequate and efficient ventilation without the aid of complicated monitoring devices.

Aids to Ventilation

The usual method for assisted or controlled respiration is by compressing the rebreathing bag of the anesthetic machine. The so-called "educated hand" is controversial, but the main advantage of this method is to obtain important information from "squeezing the bag" including presence of respiratory obstruction, compliance of the chest wall and lung to inflation, detection of spontaneous respiratory efforts indicating the need for deepening the level of general anesthesia or administering muscle relaxants.

The disadvantages are:

1. The method is inefficient and tiring

2. One is tied to the machine, though according to Dobkin and Wyant this is an advantage

3. One cannot incorporate a negative phase, though according to Cherniak this is advantageous in emphysematous patients as one cannot lower the pCO_2 in these patients to dangerous level.

Various aids to respiration and ventilation have been devised. The term "Respirator" usually refers to apparatus applied outside the body and "Ventilator" usually applies to devices attached directly to the airway. The former were considered more physiological in simultating normal respiration though Morch advocated intermittent positive pressure breathing as being preferable in patients with a tracheostomy.

Ventilators

1. *Semi-mechanical*

a. Mackintosh bellows

b. Kreissleman bellows

c. Potter foot pump

d. Ambu pulmonator

e. Etsten ventilator

f. Mackay manual respirator

These are inexpensive and Etsten's and Mackay's will very easily give pressures from plus 20 to minus 10 cm. water.

2. *Mechanical*

The ideal in mechanical respirators varies from authority to authority. The biggest controversy today involves the two types of controls; pressure controlled—volume variable; and volume controlled—pressure variable. In clinical application these are of more theoretical than practical importance.

Ventilators may be driven by electricity or by compressed gases. Basic control may be by pressure, by volume or by time. Some are controlled by combination of all three. Most respirators work continuously, but some have been devised which are initiated by the patient's respiration and provide assistance to their spontaneous efforts. So many ventilators have been introduced and their design is of such complexity that recently an excellent book, *Automatic Ventilation of the Lungs* by Mushin Baker, and Thompson has been published which describes 35 ventilators. This is a bewildering array. The main features of the most widely used are shown in *Table I.* Any of these may be satisfactory when used properly. The Jefferson ventilator, a development of the prototype of Allbritten was among the first to be fully investigated. Nealon found during open pneumothorax that ventilation was adequate and operative conditions good with pressures of plus 15 mm. Hg. and minus five mm. Hg. phases one to two. These conditions gave a mean endotracheal pressure of five mm. Hg. and mean minute ventilation of 10 litres. When the mean endotracheal pressure was three, the lungs were partially collapsed and when the mean pressure was seven the lungs were overdistended. He described the effects of other pressures.[36]

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Gilchrist's Disease

A Case Report of North American Blastomycosis

MARVIN DUNN, M.D., *and* PATRICK McCANN, M.D., *Kansas City*

NORTH AMERICAN BLASTOMYCOSIS (Gilchrist's disease) is uncommon in Kansas.[1, 2] We recently observed a patient with far advanced North American blastomycosis at the University of Kansas Medical Center. Although the disease was probably contacted elsewhere, he came to us as a patient with an undiagnosed systemic disease which was difficult to differentiate from multiple myeloma or carcinomatosis.

A case of far advanced North American blastomycosis was presented. The case was unusual because of the far advanced bony involvement and because of its occurrence in Kansas. The patient probably developed the disease in Chicago where blastomycosis is endemic.

Case History

This 54-year-old Negro male laborer was admitted to KUMC in November, 1959, with complaints of weakness, shortness of breath, weight loss, and ulcers of the face.

In January, 1959, while employed in a canning factory in Chicago, he first noted the onset of weakness and anorexia. At that time he developed a cough which was productive of white sputum. He was seen by a physician and was treated for tuberculosis for an undetermined period of time. In spite of this therapy his symptoms progressed and he noted a weight loss of ten pounds in March, 1959.

In May, 1959, a small papular lesion developed on the skin over the right zygomatic arch. This lesion ulcerated and gradually enlarged.

In July, 1959, because of progressive weight loss, anorexia, and weakness, he moved to Kansas City to live with a sister who could care for him He became short of breath and consulted a physician. Chest x-ray and several sputum specimens revealed no evidence of tuberculosis. He was digitalized and given iron tables for anemia.

Two months before admission a fungating, verrucous lesion developed over the upper lip. His symptoms continued, and by the time of admission he had lost 42 pounds of weight, could not walk, and was dyspneic at rest.

He denied a history of contact with tuberculosis or other infectious disease. He had experienced no major medical or surgical illnesses. In 1946 he received a shotgun wound. He had lived in Chicago for four years. Before that he lived on a farm in Arkansas.

The physical examination revealed a chronically ill, poorly nourished, emaciated, torpid, dysarthric, Negro male. The blood pressure was 100/65; pulse, 104 and regular; temperature, 101. Examination of the eyes, ears, nose, and throat was negative. There was a circular skin ulcer over the right zygomatic arch which was four cm. in diameter. The base of the ulcer was granular. The skin edges were discrete but neither raised nor indurated. There was a 2 x 1 x 1 cm. fungating verrucous mass over the right lip near the midline. There was no significant lymphadenopathy. Several shotgun pellets were palpable in the subcutaneous tissue of the chest. The left sternoclavicular joint was enlarged and tender. The chest excursion was decreased and the breath sounds were diminished. There were no rales. There was no dullness to percussion. A Grade III apical holosystolic murmur was present. Examination of the abdomen was negative except for the presence of shotgun pellets in the subcutaneous tissue.

Laboratory Examination

Laboratory examination revealed a hemoglobin of 7.4 grams per cent, WBC 9,900, 83 polys, 15 lymphs, two monocytes and 88,000 platelets. The VDRL was non-reactive. Urinalysis was negative. The BUN was 12 mg. per cent. Serum electrolytes were as follows: sodium, 135 mEq.; potassium, 4.6 mEq.; chlorides, 86 mEq; CO_2, 37.8 mEq.; calcium, 4.5 mEq., and phosphorus, 1.9 mEq. Histoplasmin and tuberculin skin tests were negative. The vital capacity was 1.4 liters. Bence-Jones protein was not present in the urine. Sickle cell preparation was negative. Sputa were negative for acid fast bacilli. Hepatic function studies revealed the following values: direct bilirubin, 0.1 mg. per cent; total bilirubin, 0.3 mg. per cent; alkaline phosphatase, 1.1 millimol units; BSP retention, 6 per cent; thymol turbidity, seven units; albumin, 2.39 gms. per cent; globulin, 2.54 gms. per cent;

From the Department of Medicine, University of Kansas Medical Center, Kansas City, Kansas.

Figure 1. Chest x-ray revealed an insignificant degree of pulmonary disease in spite of widespread bony disease. Note the erosion of the anterior portion of the second and third ribs on the left as well as the shotgun pellets which were lodged subcutaneously.

chlolesterol, 133 mg. per cent with 56 per cent esters. The EKG revealed myocardial ischemia.

X-rays revealed multiple osteolytic lesions of the ribs, cervical and lumbar vertebrae, and the right ilium *(Figures 1 and 2)*. Multiple myeloma or carcinomatosis was suspected. A bone marrow biopsy revealed an essentially normal marrow. A needle biopsy of the enlarged left sternoclavicular joint was performed, and Grocott stain of the tissue revealed organisms compatible with Blastomyces dermitidis *(Figure 3)*.

Before the tissue diagnosis was established, the patient left the hospital against medical advice and died at home two days later. During his hospitalization he received aspirin for pain and 2 units of whole blood.

Discussion

North American blastomycosis was first described in its cutaneous form in 1896 by Gilchrist, but was not recognized as a systemic disease until 1902.[4] The responsible organism, Blastomyces dermitidis, is a fungus with a yeast phase of development. Although the organism has been isolated for over 60 years, the mode of transmission to man is unknown.[5]

North American blastomycosis is endemic in certain areas of Michigan, Wisconsin, Illinois, and Louisiana, but is rare in Kansas.[6, 7] Because of the high incidence in Chicago, it is sometimes called "Chicago disease."[1] There is no racial, occupational, or definite seasonal distribution. Males are affected more commonly than females. Schwarz and Baum have postulated that the disease is probably systemic except in those cases where direct skin inoculation can be proved. According to their belief the cutaneous form represents a hematogenous spread from a primary pulmonary site which they consider the portal of entry. The cutaneous lesions which have been produced by accidental inoculation of infected material into the skin differ in appearance and clinical course from the cutaneous form of systemic blastomycosis. The systemic form of the disease involves the following organ systems in this order of frequency: lung, skin, bone, and genitourinary tract.

Pulmonary blastomycosis may be a subclinical[7] infection or may manifest itself as an exudative pneumonia, pleuritis, diffuse granulomatous infiltrate, or as a bronchopneumonia producing a clinical picture of low grade fever, vague chest pain, night sweats, productive cough, and hemoptysis. The pulmonary focus of infection may be radiologically insignificant even in the presence of far advanced systemic disease.

Latent Period Possible

A latent period of several weeks to several months may follow the pulmonary infection after which hematogenous spread of the disease occurs. The skin

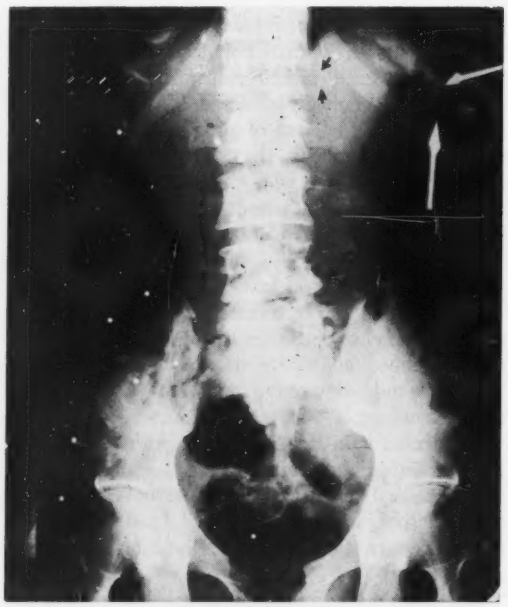

Figure 2. X-ray of the abdomen revealed osteolytic lesions of the transverse processes of several lumbar vertebrae, the 11th rib on the left, and the crest of the right ilium.

Figure 3. Tissue obtained from the left sternoclavicular joint was stained with Grocott's stain. Microscopic examination revealed multiple doubly refractile, budding organisms characteristic of blastomyces dermitidis (x 1,000).

lesions begin as papulopustular lesions which enlarge by peripheral extension and central ulceration forming elevated, erythematous, exuberant, and verrucous granulomas. There is usually a sharp border between the involved and uninvolved skin.[5]

The bony lesions are usually osteolytic involving the ribs, vertebrae, and rarely the long bones and joints. Bone marrow depression may produce pancytopenia. The genitourinary lesions consist primarily of abscesses in the prostate, epididymis, and seminal vesicles.

A positive diagnosis can be made only by culturing the organism or by identification of the organism in biopsied or postmortem tissue.

Recently excellent results have been obtained by treating patients with Amphotericin B.[5] Apparent cures have occurred in patients with far advanced systemic disease.

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Postgraduate Medicine

(Continued from page 113)

these were enrolled in correspondence courses, but this still leaves over 3,000 physician enrollments at the Medical Center. Circuit attendance increased only a small percentage. The total enrollment was 5,623 for a gain of 252. The 14 clinical traineeship enrollments represent a small but exceptionally gratifying part of the registration.

The Battenfeld Auditorium, the postgraduate offices and the other units of the Student Center-Continuation Study Building are well known to the physicians of this area as the facilities so vital to our program. We wish to mention them only to point up this prize setting for our programs.

This has been our most satisfactory year based on what we feel to have been superior teaching accomplishments, new program developments, good enrollment totals, a reduction in unit costs, and continued approval by our student body. With stability in administrative, operational and fiscal matters the program becomes even more certain of continuing to serve the medical profession in a meritorious manner.

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Color Blindness in Hunters

Because almost all color-blind persons have red and green blindness, Dr. Hubert Waldemar Lee of Brainerd, Minn., suggests that a few lives could be spared during the hunting season and perhaps on the highway if licenses were withheld for this cause. Some 4 per cent of men and 0.5 per cent of women are color blind. He points out that almost all states have rulings requiring deer hunters to wear red clothing, thus "a few of the accidental deaths must be due entirely to color blindness. In a totally color-blind person all colors vary in their degree of brightness from white through grays to black. Persons with red-green blindness are often unaware of this fact and resent being informed of it." State motor vehicle departments do not test nor withhold licenses for color blindness, he added.—*J.A.M.A.*, Nov. 21, 1959.

Cancer of the Breast

Radiation Therapy of Carcinoma of the Breast Supplementing Surgery

GALEN M. TICE, M.D., ***Kansas City***

IN OUR YEARS OF EXPERIENCE in treating malignancy we have been impressed with the change in concept relative to the correct method of treating breast cancer. During the years from 1930 to 1940 it was routine in our hospital to refer all operable breast cancer cases for radiation, usually after radical removal of the breast. Some time during the decade, 1940 to 1950, the thought was passed about in surgical circles that surgery was self-sufficient in the conduct of treatment of all breast cancer cases except the inoperable cases. New super radical operations were suggested as the answer to the breast cancer problem.

New Surgical Attitude

Handley and Thurston[3] in 1947 reported, "In five unselected cases of carcinoma of the breast, a lymph gland of the internal mammary chain was removed through the second intercostal space at or shortly after radical mastectomy. In four cases the internal mammary gland was histologically proven to contain cancer. In only two of these cases were there axillary deposits." This observation apparently suggested to the surgeons that it was possible to eliminate breast cancer metastases, if local. by surgery with no supplemental assistance from the radiologist. Our chief surgeon stopped referring his postoperative cases to us and new younger surgeons trained elsewhere, who came to our institution about this time, did not refer theirs. Our interest in radiation of the postoperative breast case was not entirely dissipated, as some surgeons apparently were not convinced that surgery alone was adequate. Over the years our referrals for radiation have not appreciably diminished, despite the changing attitude of our own staff surgeons.

Breast cancer is such a ruthless killer and is so unpredictable that any contribution by the surgeon, endocrinologist or radiologist should be viewed with critical appraisal before it is dismissed as of no value or harmful. Just as the surgeon in some instances considers his services self-sufficient, so have the radiologists in some instances indicated that their contribution is most important. At a national radiological meeting a few years ago a prominent radiologist in a round table discussion made the statement that in the operable group of cases we can expect ten per cent more five-year survivals if radiation is used to supplement surgery. We are sure that if this could be definitely substantiated there would be no hesitancy in referring these women for radiation after or before surgery. It is doubtful if any group of statistics will be acceptable to everyone, because of the many factors involved in the collecting of statistics. Unfortunately advocates of surgery without subsequent radiation, and those who advocate radiation as an adjunct to surgery sometimes become emotional in advocating their favored mode of therapy and seem not to want to see the advantages of the other modality or the disadvantages of the method they favor.

Our experience in treating breast cancer in conjunction with surgery reveals 48 per cent five year survival in Stage I and II, the operable group. This included 730 patients. If the inoperable group III and IV is included there is a total of 907 cases. The overall per cent of five year survival is 39.7 per cent.

Our series is somewhat unusual because many surgeons and only one radiologist were involved in the treatment plan.

History

Our experience in treating breast cancer goes back to 1930, 29½ years ago. We have kept quite accurate records since 1934. We do not want to clutter the literature with information and comments about something that has been described many times before, nor do we have anything particularly new to describe. We do, however, feel impelled to summarize our experience, and we will make a few comments which will largely be a review of our thoughts and those of others. There is nothing unique about these cases except that the radiation was planned and administered by one individual with the assistance of many different men in training. The surgery was done by many different surgeons. During the period from

Dr. Tice is a Professor and Chairman of the Department of Radiology, University of Kansas School of Medicine, Kansas City, Kansas.

1930 to 1955 post or preoperative cases were referred to us by 218 different surgeons, so that the results reported will have no relationship to any particular type of surgery. Most of the cases were treated by an efficient type of Halstead radical surgical procedure. Ninety cases, advanced or very aged, had a simple mastectomy followed by radiation. Radiation, even though planned and administered by one man and his residents, varied with facilities available. In 1930 the radiation was given using 140 Kvp, an open lead glass bowl, and non-shockproof wires leading off of a transformer that was used for diagnostic work for half of the day. Later a therapy couch was acquired with a porthole on top over which the area to be treated was placed. The contribution here was an increase to 200 Kvp. In 1940 the more modern orthovoltage machine utilizing 250 Kvp was made available, and during the last year a Cobalt-60 unit is being used for part of the treatment. During the last 25 years we cannot point to any one treatment machine or treatment schedule as being the answer to the breast cancer problem. We have tried to keep in touch with modern advances and have tried a few variations on our own initiative. We have treated our cases with the maximum dose of radiation available, avoiding as much as possible damage to normal structures. We have recognized that a certain amount of damage to other than tumor tissue must be an acceptable calculated risk if we are to destroy cancer cells.

Keeping a Registry

Over the years we have felt impelled, as should everyone treating cancer, to keep in touch with our patients. For many years we maintained our own follow-up system, but now we are assisted by the personnel of an efficient tumor registry. We have lost contact with 77 cases, 7.4 per cent of our total, and in our report we consider these cases dead on the last contact.

Many patients have died of diseases related to senility, some as the result of accidents, and a few due to intercurrent infections, but these are all included in the series report. For purposes of reporting we refer to Portmann's classification.[8] We have modified it by including all tumors six cm. or larger in Stage III as described by Ash.[1] Portmann's classification of breast carcinoma is as follows:

PORTMANN'S CLASSIFICATION OF BREAST CANCER

Group or Stage I

Skin ..... Not involved
Tumor ... Localized in breast and moveable
Metastases None

Group or Stage II

Skin ..... Not involved
Tumor ... Localized in breast and moveable
Metastases Few in axillary lymph nodes

Group or Stage III

Skin ..... Edematous, brawny red with induration or inflammation, not obviously due to infection, extensive ulceration, multiple secondary tumors
Tumor ... Diffusely infiltrating the breast; fixation of the tumor of the breast to the chest wall; edema of the breast; secondary tumors (Ash modification—6 cm. in diameter)
Metastases Axillary node metastases

Group or Stage IV

Skin ..... As in any other group
Tumor ... As in any other group
Metastases Axillary or supraclavicular nodes extensively involved; clinical or roentgen evidence of distant metastases

From 1930 to 1955, 907 Cases Treated

During the period 1930 to 1955, 907 cases of primary breast carcinoma were treated either pre or postoperatively or as a primary treatment, in a few hopeless, far advanced cases. During this same period 183 cases of recurrent tumor were referred for radiation. This group included bone metastasis, skin metastasis, ascites or pleural effusion, recurrent supra or axillary gland involvement, and, in a few cases, lung, liver or brain metastases. None of these cases

TABLE I

ALL CASES OF PRIMARY CARCINOMA OF THE BREAST

Stage	*Total*	*Less Than 5-Year Survival*	*Over 5-Year Survival*	*Over 10-Year Survival*	*Over 15-Year Survival*	*Over 20-Year Survival*
I	322	130	192 (59.6%)	98 (30.4%)	42 (13%)	8 (2.5%)
II	408	250	158 (38.6%)	65 (16 %)	32 (8%)	11 (2.7%)
I and II	730	380	350 (48 %)	163 (22.3%)	74 (10%)	19 (2.6%)
III and IV	177	167	10 (6 %)	0	0	0
All Stages	907	567	360 (39.7%)	163 (16.7%)	74 (8%)	19 (2 %)

TABLE II

RECURRENT CASES OF CARCINOMA OF THE BREAST*

Total	Lived Less Than 5 Years	Over 5-Year Survival	Over 10-Year Survival	Over 15-Year Survival
183	155	28 (15%)	7 (4%)	1 (0.6%)

* Metastases to bone, skin, serous surfaces, lung, liver, brain, glands.

were treated with the cobalt unit. Most of them were treated with orthovoltage, or in some cases of skin metastasis, superficial. Our results in terms of survival are listed in *Table I*.

A case of recurrent carcinoma of the breast cannot be measured in terms of longevity in most instances. These individuals with complications of metastasis as listed in *Table II* are often in great pain or mental distress. Nitrogen mustard, estrogens, androgens, and other forms of medication must certainly be used in attempting to alleviate their suffering. Despite the many new innovations for treating hopeless cancer radiation therapy still is perhaps in first place in giving pain relief. Occasionally the case with skin metastasis or metastasis to the supraclavicular glands may be given a relatively long lease on life if there is no other evidence of metastasis. Unfortunately the tumor that spreads to the bone and skin or glands often is already dissipated to other organs of the body so that early death is inevitable.

Case Longevity

In *Table II* we have listed our results in terms of longevity for cases with recurrent cancer of the breast, cases that have been operated and treated elsewhere.

In our experience only those in Stage I and II have a chance for survival. In group III and IV none had

TABLE III

PREOPERATIVE RADIATION OF CARCINOMA OF THE BREAST

Stage	Number of Cases
I	13
II	7
III	16
IV	4
Total	40

radical surgery. A few had simply mastectomy with the thought by the surgeon that a sloughing breast might be removed to make life a little more comfortable. It is our reaction that this bit of surgery might be avoided in favor of intensive radiation to the breast. If we include only Stage I and II, the operable group, our five-year survival was 48 per cent and 10-year survival was 22.3 per cent. If the relatively hopeless III and IV groups are included to make a total picture of those radiated, a group which totaled 177 cases and in which radiation was the only treatment because of the advanced stage of the disease, the five-year survival is 39.7 per cent and the 10-year survival is 16 per cent. Other statistics procured from this study indicate carcinoma in both breasts in 40 cases (4.4 per cent of the total). Cancer of the male breast was seen in 11 cases (1.2 per cent of the total). The prognosis in our series of male breast carcinoma was extremely poor. Most of the cases were far advanced when first seen. The average survival for this small group was 1.75 years. There were no five-year survivals.

Preoperative Therapy

To us an interesting facet of our survey of breast cancer relates to preoperative therapy. In 1938 the late Dr. T. G. Orr, at that time chief of the surgical

TABLE IV

SURVIVAL OF PREOPERATIVE CASES OF CARCINOMA OF THE BREAST

Stage	Number of Cases	Lived Less Than 5 Years	Lived 5 Years	Lived 10 Years	Lived 15 Years	Lived 20 Years	Still Living Over 20 Years
I	13	1	12	9	7	5	5
II	7	3	5	2	2	1	0
III	16	10	5	3	2	1	0
IV	4	4	0	0	0	0	0
Total	40	18	22	14	11	7	5

TABLE V

PERCENTAGE SURVIVAL OF THIS TREATMENT SYSTEM

	Per Cent
Five years or more survival	55
Ten years or more survival	35
Fifteen years or more survival	28
Twenty years or more survival	17.5
Living at present beyond 20 years	12.5

service at the University of Kansas Medical Center, agreed with the author to treat a series of breast carcinomas with preoperative radiation followed by surgery. Forty cases were treated in that manner, and in all but two cases biopsy was obtained prior to radiation. Surgery was done in an average time of six weeks after radiation was completed. *Table III* indicates the staging of this group of 40 patients.

Four of the cases have been lost to follow-up, and are listed as dead on the last date contacted. As in the other group causes of death other than cancer were involved in some of those dead. The survival incidence of the group is listed in *Table IV*.

Dr. David Robinson[9] reported on a survey of all breast carcinoma cases recorded as hospital patients in the University of Kansas Medical Center before 1943, and operated upon by the staff surgeons at the Medical Center. If radiation was ordered it was given by the author and his residents. It includes some of those listed in our report but does not include those referred in for radiation as outpatients operated elsewhere. Since all of the patients reported by Robinson had surgery they would fall into the Stage I and II group, and most of them would fall into the group that had surgery supplemented by radiation therapy. He reported 44.3 per cent five-year survival as compared to our report of 48 per cent in Stage I and II. For comparison we quote survival rates as reported by other investigators. Ash who is interested in preoperative therapy reports in *Table VI:*

TABLE VII

ABSOLUTE FIVE-YEAR SURVIVAL RATES IN BREAST CANCER*

Author	*Place*	*Year*	*Rate (Per Cent)*
Nohrman	Stockholm	1949	40
Smithers, *et al*	London	1952	35
Williams, *et al*	London	1953	34
Bryant, *et al*	Michigan	1954	40
McWhirter	Edinburgh	1955	42
Hickey, *et al*	Iowa	1956	36

* As reported by Murphy in his book, *Radiation Therapy.*

Murphy[6] in his book, *Radiation Therapy* lists the survival reported by other authorities. These reports are listed in *Table VII.*

Taylor and Wallace[11] reporting on 50 years experience at the Massachusetts General Hospital state, "At the present time radical mastectomy may be expected to result in a five-year 'cure' in about half of the cases submitted for operation." They did not

TABLE VI

SURVIVAL OF BREAST CANCER WITH VARIOUS TYPES OF TREATMENT AS REPORTED BY ASH, *et al*

Method of Treatment	*Per Cent 5-Year Survival*	*Per Cent 10-Year Survival*	*Type of Case*
Untreated—Daland	22	1	All untreated
Untreated—Nathanson and Welch	19	5	All untreated
SURGERY ALONE			
Collected cases	33	32	Cases selected
Excluding the categorically inoperable group—Presbyterian Hospital	50	With involvement of axillary nodes—Presbyterian Hospital, 20; Memorial Hospital, 21	Cases selected for radical mastectomy, mostly Stages I-III
Radical mastectomy and postoperative therapy—Toronto General Hospital	43	With node involvement, 23	82% Stage I-III 18% Stage IV-V
Simple mastectomy postoperative therapy—McWhirter	42	25	All cases 56% operable

routinely submit their case for radiation as a supplement to surgery. They agree, that selection of cases to be operated is a most important factor in ultimate survival statistics.

Hagensen[2] showed a survival of 74.3 per cent of Stage I with radical mastectomy, and a survival of 38.3 per cent with axillary metastasis.

Harrington[4] showed a survival of 45.4 per cent among 800 women in Stage I, II and III.

McWhirter[5] whose contribution was in the realm of postoperative therapy after simple mastectomy reported 43.7 per cent five-year survival. Seventy-seven per cent of this series had metastasis.

Nathanson and Welch[7] reported 25 per cent dead in the first year out of 100 cases of breast carcinoma that were not treated; an additional 25 per cent died in 2.5 years; 25 per cent lived over four years. In a series of 1,550 treated cases 75 per cent died in 6.5 years. In five years there were 25 per cent more alive in the treated cases than in the untreated cases. The average length of life from the patient's knowledge of the onset of disease was 3.5 years in patients treated in the years 1912 to 1932, compared with 2.5 years in the untreated group.

Cancer Cases

We are faced with the statistical evidence that there is not much diffierence in the five-year survival in patients with breast carcinoma as reported by various observers. There are many intangible factors to consider. Case report No. 1 illustrates the patient who lived with her cancer for many years, and she is still living. It would be difficult to say that she is alive because of either surgery or radiation. Either she had a slowly growing carcinoma that metastasized slowly and grew indolently, or her inherent resistance of the tumor bed to tumor expansion was such that she tolerated the tumor better than the average case. We are sure that in many cases of longevity this inherent resistance to the growth of the tumor is an important factor. Pregnancy in the past has been considered an exciting factor in tumor growth. In our experience pregnancy has not been in the average case a factor producing rapid rate of tumor growth.

Case I

Our first contact with this 73 year old patient was in June, 1954. She gave a history of having had right mastectomy on June 23, 1930 in a hospital in Kansas. A diagnosis at that time of scirrhous carcinoma of the breast was made. This was a simple mastectomy.

In 1948 she noticed a nodule in the right axilla. This was removed at the University of Kansas Medical Center. A diagnosis of infiltrating adenocarcinoma of the right axilla was made.

In 1954 on our first contact a nodule was found in the right supraclavicular area. This was biopsied and was reported metastatic nodule in the supraclavicular area. At that time radiation therapy was given to this supraclavicular area.

In February, 1959, she returned with a tumor mass measuring 4 x 2 inches in size attached to the right posterior axillary fold. There was a nodule 1 cm. in diameter on the upper right chest wall. The solitary nodule was treated with 5,000 r. as we would treat a skin cancer. The mass on the posterior axillary fold was treated with oblique portals, cross firing for a dose of 5,155 r. depth dose. The skin nodule disappeared rapidly. The large posterior axillary mass disappeared slowly. This was last seen on November 30, 1959. At that time the posterior axillary mass was a warty mass about two cm. in diameter. It had not completely disappeared. Chest examination showed no intrinsic lung disease. The supraclavicular area showed small hard glands not over .5 cm. in diameter. The patient was feeling quite well. She is now 79 years old.

This case is reported to show the variation in tumor growth and tumor spread. The patient was diagnosed and treated thirty years ago for a cancer. She was not followed by radiation at the time of original operation or the second operation for the axillary node. Radiation was given when the supraclavicular gland was diagnosed six years ago. We do have definite evidence that there has been destruction of the tumor in the posterior axillary fold. One can only surmise that if she had had radiation at first in 1930 she might not have had the subsequent recurrence described. This is a matter of conjecture only.

Radiation Destroys Cancer Cells

Even though we as radiologists cannot quote conclusive figures to justify the surgeon sending his postoperative cases to us for radiation, there are certain facts that would seem to justify this procedure in all except the case of the tumor with a small moveable mass in the breast and no axillary glands. Even here there might be a reason for postoperative therapy because of our inability clinically to recognize cancer involved glands in every case by palpation and inspection. Saphir and Amromin[10] were able by meticulous care to find cancer cells in 30 per cent of glands reported as free from cancer by routine examination. It seems to us that there are bits of evidence that breast cancer may be destroyed or temporarily controlled by irradiation. Where there is visible cancer on the chest wall, perhaps related to an inoperable breast malignancy or recurring nodules on the chest wall these obvious tumor masses may be made to disappear with proper radiation. The patient with bone metastasis diagnosed by clinical findings and x-ray examination will get pain relief, and, in many instances, subsequent examination will show that areas of bone loss have been replaced by deposition of new calcified bone. We are most impressed by the cases that have received preoperative radiation. The biopsy of tumor

tissue prior to radiation makes the diagnosis of cancer. The study of tissue removed after radiation at the time of surgery almost invariably is reported by the pathologist as showing changes due to radiation. He may report complete disappearance of tumor, or he may indicate that there are shrunken, damaged tumor cells. In the tumor bed reports are made of hyalinization, fibrosis and endarteritis. Case II is given to show the pathological change in the tumor following radiation.

Case II

This 51 year old white female was admitted on March 2, 1938, for biopsy. She had previously reported a lump in her breast which had been present for thirteen months. This lump was located in the upper outer quadrant of the right breast. It was hard, nodular, and freely moveable. It measured 3 cm. in diameter. Biopsy was taken on 3-3-38. The mass was not completely removed. Two bits of tissue measuring 2 x 1.5 x .8 cm. and 1.5 x 1.5 x 1 cm. were submitted to the pathologist. The path report in part is as follows: "Large irregular sheets and masses of epithelial cells often infiltrated into the adjacent tissue and showing a scant amount of stroma can be recognized. This latter tissue has the appearance of medullary carcinoma. Diagnosis: Medullary carcinoma of the breast."

In a period of one month the patient was given radiation to the glandular areas. The breast and chest wall were treated with a cross fire application of x-ray. Examination of the breast on May 13, 1938 prior to surgery was as follows: "Examination of the right breast at the time of admission showed a healed biopsy scar in the upper outer quadrant. The underlying tissue was somewhat indurated, however, there was no definite tumor tissue present. No glands were palpable in either axilla or supraclavicular areas." Radical breast surgery was done by Dr. T. G. Orr on 5-16-38. Path report on this patient is in part as follows: ". . . On one side of the nipple is seen a small well healed surgical incision. . . . This incision may be palpated as a definite tumor mass, somewhat irregular in contour, measuring about 4 x 5 cm. in diameter. Sections of the mass which is firm and rubbery reveal a fibro cellular-like tissue which shows no definite architecture. It is rather diffuse. . . . The tissue cuts with considerable resistance. The normal architecture of the breast appears to have been destroyed. In the axillary plug . . . is no evidence of metastasis. However a larger nodule—on cut section has somewhat of a gray cellular-like appearance presenting no definite architecture. The latter is suggestive of tumor metastasis." Histological pathology: "Diagnosis, post-x-ray sclerosis of a breast carcinoma with a few shrunken tumor cells still present; chronic lymphadenitis."

This report is not unique. It is true that in some of the cases the entire one or two cm. tumor was removed. That was not true in this case. In this series of forty cases treated with preoperative radiation the following notation was made by the pathologist 18 times: "shrunken, atrophic, or unrecognizable tumor cells." In 25 reports the note was made that there was hyalinization, fibrosis or endarteritis."

This patient was operated in 1944 for carcinoma of the bladder and later for carcinoma of the cecum. She died on September 16, 1951, 13½ years after the breast tumor was diagnosed and removed.

Conclusions

A series of 40 cases received radiation before surgery. In this group there were 55 per cent who survived five years or more; 33 per cent, 10 years; 28 per cent, 15 years; and 17.5 per cent, 20 years. It would seem logical to make this a standard procedure.

It is most difficult to compare series of cases reported with different plans for management and with different degrees of tumor development and spread. There is evidence that cancer may be destroyed by irradiation. There is evidence that fibrosis, hyalinization and endarteritis may alter the tumor bed to theoretically interfere with tumor spread. We cannot statistically prove that radiation therapy, at least postoperatively given, will increase survival rates; preoperatively given perhaps it does. When we see the direct effect of radiation on primary tumor and metastatic deposits in skin and bone we feel it should be used routinely as an adjunct to surgery. We suggest that it should be used more often preoperatively.

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Corrective Bowling

From a Scientific Approach

DR. TUNG N. CHEKE,* ***Kansas City***

THERE HAS BEEN INCREASING emphasis in recent years, as the thoughtful reader of editorials has undoubtedly noticed, on recreation for physicians. Practically everything from chess to taxidermy has been recommended at one time or another. Bowling has also been mentioned, it is true, but always the stress is on fun and socializing. I say, let's talk about the *science* of bowling.

Most bowlers have such a good time that they often neglect to analyze and correct their bowling faults; consequently, they never attain a truly professional status. I have developed a system which is guaranteed to eliminate bowling errors of technique. My system has a remedy for any bowling "ailment." These are numerous, but fall into one of the following categories: (1) approach, (2) swing and release of ball, and (3) aim and pinfall. You will no doubt be interested in the following examples taken from my Pilot Program, in which I systematically analyzed and corrected the faulty techniques of the other members of my bowling team. I completed this initial project during the final month of the last league season and, if I may say so, with rather remarkable results. As you, too, may wish to use my corrective bowling system on your teammates (as well as improve your own style), I will describe briefly the process used.

Watch That Approach

First, approach. Ed had undoubtedly the worst approach of any man on the team, so I began with him. As he had short arms, he tried to increase the speed of the ball by using a fast five-step approach, often sliding right across the foul line. You may have heard the bell and seen the red light flash in your own league, as someone crossed the foul line. With my system, this never happens. I simply instructed Ed to take his five steps *on his knees!* This is so basic and simple that, like all great ideas, you wonder why no one ever thought of it before, don't you? And the beauty of it is that it really works. Not once did Ed ever cross the foul line using my system of approach. I am really sorry that he didn't stick with this system, as I am sure that his knees would have toughened in time and I still feel that the plastic surgeon was a little premature in applying the skin grafts.

Second, swing and release of the ball. It is well known to all bowlers that a good backswing increases the power of the ball as it is released. My system utilizes this essential point. Instead of the conventional method of holding the ball with both hands at the chest level and swinging down, back, then forward as you make the approach, do it the scientific way—as I told Wilbur. I instructed him to start with the ball hanging down at his side, then swing it forward (instead of backward) and allow the weight of the ball to carry it up and *overhead* and back, making a full circle with the ball. When the ball comes down and forward again, it has *real* power! Naturally, this requires a firm grip at all times, as release of the ball on its downward descent could seriously disable the end man on the bench. However, Wilbur was always a little clumsy, and I am sure that, once the lawsuit is settled, he will be more cautious when he begins to bowl again and will hold the ball more securely.

Keep a Sharp Eye

Third, aim and pinfall. This, after all, is the factor that causes the points to add up to a good score. I find that many bowlers do not follow through sufficiently. Herb was a good example of poor follow-through. He was, however, an excellent student and corrected this fault on his first lesson from me. My scientific system was again proved effective. I simply instructed him to lean farther forward as he released the ball, and not just from the waist but starting with the ankles. In this way, the entire body participates in a smooth follow-through. Using my system for the first time, Herb was able to throw a ball with a perfect hook, hitting the 1-3 pocket squarely, and resulting in a *strike!* He may even have given the ball a shade too *much* follow-through, as I explained to him in the hospital afterwards. Incidentally, those of you who know Herb might do well to just sort of ignore the subject of his nose, although actually it

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Department of Physical Medicine, University of Kansas School of Medicine.

* We are well aware that the American Medical Association has recently recommended that the use of the term "doctor" be dropped in signatures, titles, etc., but we are faced with a rather unusual situation here, in that Dr. Cheke answered our inquiry in this matter with the information that the only degree he had ever been able to acquire was a second degree, occurring when he inadvertantly picked up a lighted cigarette by the wrong end.

Editor's note: We are indebted to Marilyn K. Hutchison, M.D. for translating this article from the original which was a composite of pidgin English and lingua franca.

"Liver Function" Tests

Interpretation and Use of Various Methods

ROBERT T. MANNING, M.D., *and* MAHLON H. DELP, M.D., *Kansas City*

THE NUMBER OF LABORATORY procedures which have been proposed as "liver function" tests has become too numerous to recount. This simple observation should emphasize that there is no "liver function" test available. All tests presently in use are indirect measurements of one or more aspects of liver metabolism, and in addition are not infrequently altered by disturbed physiology outside the liver. The multiplicity of metabolic activities of the liver further limits the usefulness of any single test as a means of assaying altered hepatic metabolism. Despite their limitations, however, certain tests have proven of value both in diagnosis and prognosis.

Selection of Tests

As outlined, the many functions of the liver preclude use of any single test as a means of defining liver pathology. Certain tests, however, may conveniently be grouped as indicated in the accompanying tables for the purpose of more direct application to the problems of *detection, differential diagnosis* of jaundice, and *prognosis* in liver disease.

Repetition of tests is of considerably more value than single values. Weekly assay of such tests may be of particular value in obscure liver pathology and prognosis.

Excretory Function

Bilirubin—urobilinogen. Some of the details of bilirubin excretion have been elucidated in the past three years. Bilirubin, produced incident to normal red cell destruction, is carried to the liver where it is conjugated with glucuronic acid and excreted into the bile. The unconjugated free bilirubin is identical with the delayed or indirect fraction of old terminology and the direct, prompt or one minute fraction is essentially bilirubin glucuronide.

It follows, therefore, that bilirubin accumulates in the blood, and clinical jaundice appears wherever the capacity of this conjugating mechanism is overwhelmed. This may occur when a normal liver receives an excessive influx of bilirubin as with a hemolytic process. Free bilirubin accumulates and a sharp rise of the unconjugated fraction is reported on laboratory study. On the other hand, even normal quantities of bilirubin cannot be handled by a liver functionally impaired by hepatitis or biliary obstruction. Here, both unconjugated bilirubin and bilirubin glucuronide accumulate in the serum, free bilirubin rising because of impaired conjugation in the damaged cells and bilirubin glucuronide increasing by leakage from injured cells and ruptured bile ductules.

Recent advances have clarified the mechanism of some commonly used tests of liver disturbance. Unfortunately, all such tests are indirect measures of the multiple function of the liver. As such, they are seldom diagnostic of any specific lesion. A few tests have proven of particular value and have been outlined. Combinations of these measurements, repeated at intervals, may be of considerable assistance in the differential diagnosis and prognosis of the patient with jaundice.

Any test or group of tests do not replace classic clinical investigation by history and examination; they are additional only, and unfortunately are all too frequently of no great assistance.

The bilirubin glucuronide excreted by the liver enters the intestine where it is altered by the normal bacteria flora to urobilinogen. The urobilinogen thus formed inparts the normal brown color to the stool. Consequently, any factor that reduces the amount of urobilinogen formed leads to the passage of the characteristic clay-colored stool of hepatic disease. The most common causes are diminished bile flow due to functional impairment of liver bile production, *i.e.,* viral hepatitis and extrahepatic obstruction of the common duct, as in carcinoma of the pancreas. Simple observation of the stool color, therefore, is an excellent means of assessing liver function. More precise information may be gained by quantitative measurement of fecal urobilinogen. Levels of less than five milligrams per 24 hours are indicative of total extrahepatic bile duct obstruction. Conversely

Dr. Manning is an Associate in Medicine and Dr. Delp is Professor of Medicine at the University of Kansas Medical Center in Kansas City, Kansas.

TABLE I

DETECTION OF LIVER DISEASE

1. Bromsulphthalein excretion
2. Urine urobilinogen
3. Cephalin cholesterol flocculation
4. Transaminase
5. Serum bilirubin

increased excretion of bilirubin as occurs with hemolytic disorders leads to high levels of fecal urobilinogen, a most important finding in confirming the diagnosis of hemolytic phenomena and in the differential diagnosis of jaundice.

A small quantity of the urobilinogen formed in the intestine is absorbed and is subsequently excreted by both the liver and the kidney. The hepatic excretory mechanism is impaired early with liver injury, and, as a result, increased quantities of urobilinogen appear in the urine in patients with liver disorders. The simple test is a good one for screening patients for the presence of liver disease.

Two Notes Made

Two notes should be made with regard to the previous discussion: (1) broad spectrum antibiotic therapy reduces the value of urobilinogen determination since it reduces or alters the intestinal flora necessary for urobilinogen formation; (2) absent fecal urobilinogen combined with increased urine urobilinogen levels may paradoxically be found occasionally. This is usually associated with total bile duct obstruction and a cholangitis due to coliform organisms.

These tests relative to the total metabolism of bilirubin are, therefore, of value in detection of liver disease and in the differential diagnosis of jaundice. Measurement of serum bilirubin also has some advantage in prognosis of patients with liver disease. Persistent high levels of total serum bilirubin, particularly when associated with high levels of bilirubin glucuronide, are a sign of persistent hepatocellular injury. Chemical recovery is usually heralded biochemically by increasing quantities of urbilinogen in the stool and a later decrease in serum bilirubin towards normal.

TABLE II

DIFFERENTIAL DIAGNOSIS OF JAUNDICE

1. Alkaline phosphatase
2. Fecal urobilinogen
3. Transaminase
4. Serum bilirubin

Bromsulphthalein (BSP) Excretion. Of all the tests of liver metabolic activity, the measurement of bromsulphthalein excretion is probably the most sensitive and the single best test for detection of disturbed liver function. It is of little value in differential diagnosis. It is usually not performed in the presence of jaundice, since the factors which produce retention of bilirubin in turn produce bromsulphthalein retention in the serum.

Bromsulphthalein excretion is dependent on the amount of blood reaching from the liver cells and, as such, may be altered by factors which influence hepatic blood flow, such as congestive heart failure and shunting within and without the liver, as in portal hypertension. Recent research has produced considerable evidence that bromsulphthalein is conjugated with glutathione or derivatives of glutathione for excretion in a manner quite analagous to the conjugation of bilirubin with glucuronic acid.

TABLE III

DIFFERENTIAL DIAGNOSIS OF JAUNDICE

	FB	*BG*	*AP*	*FU*	*SGOT*
Viral Hepatitis	+++	++++	N+	N–	++++
Biliary Obstruction	+++	++	++++	–	+
Hemolytic Disease	++++	+	N	+++	N

FB = Free bilirubin
BG = Bilirubin glucuronide
AP = Alkaline Phosphatase
FU = Fecal urobilinogen
SGOT = Transaminase

Abnormalities of Protein Metabolism

Quantitative determination of serum albumin and globulin as well as *protein electrophoresis* are direct measurements which may accurately reveal protein disturbances frequently seen in liver disease. All turbidity and flocculation tests are really indirect assays of quantitative and qualitative protein abnormalities. They are not, therefore, diagnostic of liver disease, *per se.*

The *cephalin cholesterol flocculation* and *thymol turbidity* tests commonly used possess no distinct advantage over other similar reactions. They are commonly abnormal in primary parenchymal cell disease; less often in obstructive disorders. The CCF test is an adequate screening test for viral hepatitis. During the course of viral hepatitis the CCF usually returns to normal before the thymol turbidity.

Enzyme Measurements

Measurement of serum activity of various enzymes has been advanced considerably in recent years, but the

number of tests is far too lengthy to consider each individually and indeed no single test has proven of distinct diagnostic advantage over the others. For reasons of ease in performance and application in other disorders, measurement of *serum glutamic—oxalacetic transaminase (SGOT)* and *alkaline phosphatase (AP)* activity are presently the most useful, even though not the most specific for liver cell injury.

Serum glutamic—oxalacetic transaminase. Values of SGOT over 1,000 units are strong evidence of hepatic cell necrosis. Such levels are most commonly found in viral hepatitis during the acute phase, and a return of SGOT levels towards normal heralds clinical recovery. A secondary rise of SGOT activity frequently presages a relapse calling for further bed rest and supportive therapy. The test also has value in differential diagnosis, since serum activities are seldom increased over 500 units in patients with biliary obstruction. In interpreting any of these values, care must be taken to eliminate myocardial and skeletal damage as a cause of the elevation, since these tissues also contain considerable quantities of the enzyme.

Alkaline phosphatase. Measurement of alkaline phosphatase activity has stood the test of time and is of particular value in differential diagnosis of liver disease. Values over 8 mM units (method of Bessey-Lowry-Brock or 15 Bodansky units are quite uncommon except with biliary obstruction, either extrahepatic from stone tumour or stricture, or intrahepatic as from chlorpromazine. Rarely viral hepatitis produces an obstructive picture which can be extremely confusing *i.e.,* cholangiolitic hepatitis.

Elevation of serum alkaline phosphatase is frequently noted in focal lesions within the liver such as metastatic carcinoma or granulomatous infiltration *(i.e.,* sarcoid, tuberculosis, histoplasmosis). Indeed, the finding of high serum alkaline phosphatase activity in the absence of jaundice or other prominent signs of liver disease is strongly suggestive of metastatic disease of the liver, particularly if associated with increased levels of gamma globulin.

Miscellaneous Tests

Of the many other tests which have been used for assaying liver dysfunction, a few others are of use for specific points.

With respect to detecting liver cell injury, *serum iron* measurements are a proven value and should not be neglected. Values over 300 micrograms per cent, are very uncommon except in patients with viral hepatitis. Measurement of serum iron is of additional value in detecting the presence of hemachromatosis.

Persistent *prothrombin time* depression in the absence of bile duct obstruction is a sign of poor prognosis. The response of prothrombin activity to parenteral administration of vitamin K is occasionally of value in differential diagnosis. Lack of response indicates severe parenchymal cell dysfunction while a return to normal following vitamin K is usually seen with obstructive disorders.

TABLE IV

PROGNOSIS IN LIVER DISEASE

1. Serum bilirubin
2. Transaminase
3. Cholesterol
4. Cephalin cholesterol flocculation
5. Prothrombin time

Measurement of *total cholesterol* and *cholesterol esters* also have value in prognosis, since low levels of total cholesterol are frequently associated with a poor outcome. The per cent of cholesterol which is esterified is usually depressed in the presence of jaundice. However, marked depression of per cent cholesterol ester (<20 per cent) is sign of severe injury, particularly if associated with a serum bilirubin of less than five milligrams per cent. Also, high total cholesterol levels are uncommon in Laennec's or post-hepatitis cirrhosis, but are quite common in biliary cirrhosis.

Corrective Bowling

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looks better than before, because you know how quick-tempered old Herb can be sometimes.

It's Not Without Some Hazards

One final word: expect your score to drop slightly as you change over to the scientific system of bowling, then to pick up by a similar amount as you perfect the technique. For example, you may drop down five points, then go over your former average by five points. One fellow I know has just started following one of my suggestions and already his score has dropped from 180 to 119. Think what a terrific score this man will have when *he* recovers double the lost points! I am bowling with a new league this season, by the way. Funny the way it happened. The other fellows thought for awhile that they wouldn't be able to make it on Monday nights, for various reasons, but after I had already joined a new team they found that they were going to be able to bowl together after all. Too bad they will have to find a replacement for me, but this new team is showing some serious errors in technique and I feel obligated to stay with them until I can straighten them out.

Psychiatry Today

The Influence of Current Psychiatric Trends On General Practice and the Community

MERRILL T. EATON, JR., M.D.; JOHN T. BRAUCHI, M.D.; *and* DONALD C. GREAVES, M.D., *Kansas City*

- **The development of open ward care for psychotic patients, changing relationships between psychiatry and the law, new medications, and improved psychotherapeutic techniques will make possible the treatment of more psychiatric patients in their own communities.**
- **Community participation will include the establishment of psychiatric treatment facilities in general hospitals, the development of community mental hygiene clinics, and the development of other social agencies for the mentally ill and aged.**
- **General practitioners will be able to treat more psychiatric cases successfully and will give increasing attention to psychiatry and geriatrics.**
- **Efforts are being made to improve the teaching of psychiatry to medical students, specialists, and general practitioners and to relieve the shortage of psychiatrists.**

AMONG THE RECENT developments in psychiatry which are likely to have profound effects upon the roles of general practitioner and the community in the treatment in mental illness are: (1) the movement toward the care of psychotic patients on open rather than on closed or locked wards; (2) modifications in the relationship of psychiatry and the law; (3) improved understanding of the problems of the aged and aging; (4) the introduction of new medications; (5) improvement in psychotherapeutic techniques and methods of teaching psychotherapy; (6) expanded programs of post-graduate and residency education in psychiatry.

These developments and their probable consequences will be discussed on the basis of the authors' experience in the Department of Psychiatry at the University of Kansas Medical Center.

Open Wards

The development of the open ward would appear at first thought to be a major interest only to the staffs of psychiatric hospitals and their patients. However, it is of more general significance. For many years a majority of the patients having the more serious psychiatric disorders were treated on locked wards with special custodial features such as detention screen on the windows and seclusion rooms. This contributed to a restrictive, unpleasant, and authoritarian environment. Unlocked or open wards were limited chiefly to a few wards for convalescent patients in the larger hospitals and to wards caring for minor psychiatric syndromes. In recent years T. P. Rees[8, 9] and others have rather conclusively demonstrated that most, if not all, psychiatric patients can be treated on open wards. Much of the early experience with the open ward was in large mental hospitals in this country and abroad. These hospitals differ from the psychiatric wards of general hospitals in that a number of patients are chronic; the turnover of patient population is slower; and, in addition, the location and grounds of many psychiatric hospitals offer both privacy and recreational facilities for patients. More recently it has been demonstrated that the open psychiatric ward is also practical in the general hospital.

The conversion of the psychiatric ward at the University of Kansas Medical Center to an open ward was reported by Dr. Kisik Kim and Dr. Merrill T. Eaton, Jr.[6] Since that time, as part of a planned expansion, bed capacity in the department has increased from thirty-three to forty-two. Open ward operation has continued to be satisfactory. For the general practitioner and the community the importance of the open ward lies not only in the fact that it is more pleasant for patients and their relatives, but that it has certain therapeutic advantages including improved cooperation and the psychological benefits that accompany the sense of dignity, responsibility, and self-esteem which a patient may have on an open ward.

From the Department of Psychiatry, University of Kansas School of Medicine, Kansas City, Kansas.

Dr. Greaves is Professor and Chairman of the Department of Psychiatry; Dr. Eaton is Associate Professor; and Dr. Brauchi is an Instructor.

One in Ten

Since at least one person in every ten is treated in a psychiatric hospital at some time in his life, and since nearly all of these patients are first seen by their family doctors, changes in treatment facilities become important to the practitioner. The open ward should make it easier for patients and their families to accept a recommendation for hospitalization when this proves necessary. Moreover, the practicality of the open ward simplifies the problem of the creation of facilities for the care of psychiatric patients in the general hospitals of the smaller communities. The creation of more psychiatric wards in general hospitals will give the practitioner a better opportunity to treat his own psychiatric patients and to keep in touch with those cases whom he refers to a specialist. Local facilities will keep the patients in better contact with their families, friends, employers, and the rest of the community. This can be expected to speed recovery and facilitate rehabilitation. Since locks, detention screens, and special windows and doors are no longer necessary, the creation of a psychiatric unit in a general hospital should not be much different and certainly no more complicated or costly than the addition of beds for any other type of patients. Seclusion rooms are not needed. At the University of Kansas Medical Center seclusion rooms have been converted to offices.

Since psychiatric patients may generally be up and dressed during the daytime, some living room space is desirable as is an area for occupational therapy and for recreation. Patients may eat in a dining room. This requires the construction of a special facility that in the long run should be more economical than serving from trays in the rooms. Dining room, living room, and recreational facilities may be shared by men and women patients and, in fact, this offers some advantage since it leads to patients giving more attention to grooming and deportment. Even if the minimum special construction and assignment of space recommended here is impractical, psychiatric patients can be treated on general medical and surgical wards.[1]

Psychiatry and the Law

There have been some recent changes in the relationship of psychiatry and the law. One of these is closely related to the development of the open ward. The locked ward, which in effect deprived the patient of certain personal liberties, often made it a medico-legal necessity to obtain commitment or court order before confining the patient. Even should the patient accept care on a locked ward on a voluntary basis, a formal written consent was usually necessary. The existence of the legal procedure of commitment or court order added to the physician's responsibilities and complicated the reaction of the patient. Implicit in commitment is the idea that the patient is irresponsible, although many quite sick psychiatric patients are capable of exercising responsibility. On an open ward the patient is not confined. He may leave, though, as in any other part of the hospital, efforts will be made to dissuade him from doing so if it seems unwise or harmful. Court order or commitment is rarely necessary and in its absence the physician can devote greater attention to his real responsibility, the treatment of illness, and less to functioning as a sort of guardian to the patient. This will simplify the creation and operation of psychiatric facilities in the general hospitals.

Another facet of the relationship between psychiatry and the law is the question of legal responsibility in crime. There is no reason to believe that crime is more frequent among the mentally ill than in any other population group. However, for some patients a crime can be the product of illness. Kansas statutes concerning criminal responsibility are based fundamentally upon the McNaghten rules formulated by the British House of Lords in 1843. Medical science and the understanding of mental illness has increased vastly since 1843, but the basis for the law has remained unchanged. The fundamental feature of the McNaghten rules is the question of the patient's ability to discriminate between right and wrong. Though some authors regard this as a relative concept, allowing for some leeway in interpretation,[4] it is quite possible for a practitioner, called upon as an expert witness, to be in the awkward position of knowing that a patient has a serious psychiatric illness and that the illness produced a crime, but having to testify that the patient is legally sane because he knew an act to be wrong and knew its consequences. The Durham decision in the District of Columbia courts points the way to a more reasonable approach to criminal responsibility. In essence, it does not raise the question of knowledge of right and wrong, but instead the question of whether the crime is the product of illness. It is probable that in coming years laws recognizing this test of criminal responsibility will be enacted in many of our states. When this becomes true, the practitioner may testify in a criminal case on medical grounds rather than on a legal technicality. This will, however, create one new problem in connection with the trend toward open wards in psychiatric hospitals since if a patient should be found not guilty by reason of insanity, it must then be determined whether he should be treated on an open ward, or whether he indeed requires custody in addition to treatment.

Old People Admitted

A large number of elderly patients are admitted to mental hospitals. It should be anticipated that this

number will be reduced in coming years. Senile psychotic reactions and brain syndromes associated with cerebral arteriosclerosis are not necessary concomitants of aging. Improved general medical care of the aging patient and special attention to nutrition are among the prophylactic steps possible. Vitamin B_{12} deficiencies may play a part in some cases.[3] Special attention is now being paid to the role of hearing difficulties in the development of some psychiatric disorders in the aged patient. The advantage of continued constructive activity following retirement has been recognized and it is part of the function of the physician to assist his patient in making reasonable retirement plans. Continuation of an active social life into advanced years is also sound mental hygiene. Cooperation between physicians and social agencies may be helpful, both in assisting patients with retirement plans, and in assisting them to maintain an active social life. Psychotherapy is frequently indicated in both the adjustment reactions of late life and brain syndromes associated with senile brain disease or cerebral arteriosclerosis.[7] Its use should be considered even in cases in which there is evidence of considerable damage to the central nervous system and in which there are associated disorders of other systems.

New Medications

A number of new medications for use in psychiatric illnesses have been introduced in the past few years. Several of these have been studied intensively at the University of Kansas Medical Center, and at present a research project on anti-depressant medications is in progress. These new preparations, most of which are sedatives (tranquilizers) or stimulants (energizers), are not specific for particular syndromes nor are they curative, but instead are symptomatic. Their proper use, however, permits many more patients to be treated as out-patients than could previously be managed without hospital care, makes some out-patients and in-patients more approachable, and is adjunctive to the over-all psychotherapeutic program.[5] Since a large number of pharmaceutical houses have entered this field, the practitioner must learn about a vast number of new drugs. It is important to base the prescription of these drugs upon clinical findings, rather than the patient's unsupported description of his symptom. Some patients will describe themselves as experiencing anxiety, when actually they are having some other unpleasant affective state; others may describe "depression" that actually shows to be loneliness or boredom. The tranquilizers are most useful when objective evidences of anxiety, tension, or agitation are present. Likewise it is important to observe objective evidences of depression before prescribing the energizers. Nearly all of these products have numerous side effects, some of which are serious, and it is important to be aware of them.[2] Patients receiving these new medications should be followed closely, not only because of the possibility of side effects, but also because of the risk that the symptomatic medication will conceal symptoms and mask a dangerous progress of illness.

These drugs are already widely used in general practice and since they add to the number of patients who may be treated as out-patients, they increase the number of psychiatric cases who can be treated by general practitioners in their own communities.

Psychotherapy First Choice

Psychotherapeutic interviews remain the treatment of choice for a majority of the psychoneurotic and psychotic reactions. Many effective techniques of psychotherapy are long term and accordingly expensive, but a constant effort is being made to develop and improve techniques of brief psychotherapy. The teaching of psychotherapeutic technique has long been a difficult problem. Like all techniques, this must be learned by demonstration and by performing therapy under supervision. Effective instruction in psychotherapy must include continuous supervision of some cases from the first interview until the completion of therapy; it cannot be based on single interviews or short series of appointments alone. For many patients it would be quite impractical to expect long and intensive discussion of personal problems with an audience of medical students or physicians in the room. Demonstration or supervision based upon notes taken in a private interview invites some inaccuracy and distortion. If tape recordings are used, facial expression and gestures cannot be conveyed. However, patients who would be made uncomfortable and unable to discuss their problems readily with an audience in the room, are able to do this before a one-way vision mirror or a television camera even though they are aware that there is an unseen audience. At the present time closed circuit television is being used as a means of instructing resident physicians in psychotherapeutic technique at the Medical Center. Though television has been used to demonstrate psychopathology and diagnostic problems to the undergraduate medical student, it has not yet been used to teach therapeutic technique below the resident level. However, a project for this is under active consideration and will be instituted at the University of Kansas Medical Center when funds and equipment are available. It is only one step from this to the application of this teaching method in post-graduate instruction.

Psychiatric Disorders High

The incidence of psychiatric disorder is high. The supply of psychiatrists is low and these are concen-

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Oral Hypoglycemic Agents

Clinical Experience With 50 Diabetic Patients

ROBERT E. BOLINGER, M.D.; WU-HAO TU, M.D.; *and* CHARLES KENDALL, M.D., *Kansas City*

Experiences with management of 50 diabetic patients with oral hypoglycemic agents is reported. A good response was obtained in about half of the patients treated with the sulfonylureas and failure occurred in about one-fifth of the cases tried. The incidence of successes increased after age 45 and in patients taking less than 20 units of insulin. Several incidences of refractoriness to one of the sulfa drugs and responsiveness to another were noted. DBI had the additional advantage over the sulfonylureas in being effective in combination with insulin in young, "brittle" diabetics.

Reactions to be guarded against with the sulfonylurea drugs are hypoglycemia and ketosis in refractory patients.

EXPERIENCE IN THE diabetic clinic with the use of the oral hypoglycemic agents in 50 patients is reported in this paper. The patients were followed on an out-patient basis with periodic determination of the fasting blood sugar and a urine glucose. The severity of the diabetes among the patients was graded as follows:

Severe	7
Moderate	18
Mild	25

What Drugs Are Available for Oral Hypoglycemic Therapy

The drugs which have proven hypoglycemic activity fall into two groups: first the **sulfonylureas,** which in this series include tolbutamide,* chlorpropamide,** and metahexamide; and second, the **diguanides,** the only representative of which is used here is phenformin (DBI).

The sulfonylureas are handled by the body in much the same manner as the sulfa drugs used clinically for their antibiotic activity. These drugs are absorbed rapidly from the gastrointestinal tract and excreted slowly after conjugation and alteration in the body, such that measurable blood levels are present for several hours after a single dose. The sulfa drugs differ from one another mainly in their rate of excretion such that the time for half of the drug to disappear from the blood is as follows *(Figure 1)*:

	Hours
Tolbutamide	4.7
Chlorpropamide	35
Metahexamide	26

These drugs produce an immediate hypoglycemia, the degree of which depends on the blood level of the drug and on the particular drug used.[2, 3] As measured by the blood level of the drug necessary to produce hypoglycemia, metahexamide has been rated from two to seven times as potent as tolbutamide.[2-4]

The handling of DBI in the body is not thoroughly understood. It does not produce consistent blood levels and as far as is known does not accumulate in the body as do the sulfa drugs. A part of it is excreted into the gastric juice.[5]

The sulfa drugs by virtue of the fact that they maintain blood levels for long periods of time can

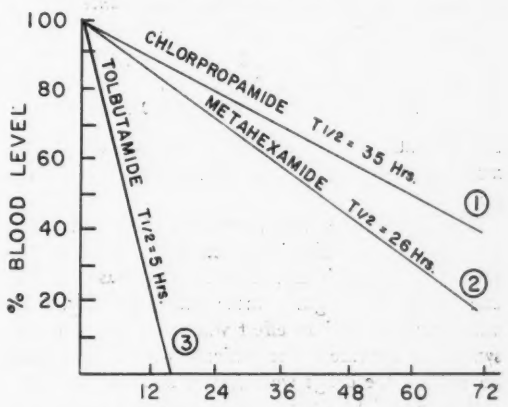

Figure 1. Rate of disappearance of sulfonylureas from the blood. (Compiled from the literature.)

From the Department of Medicine, University of Kansas School of Medicine, Kansas City, Kansas. Supported by Grant-in-aid, U.S.P.H.S. Dr. Wu-Hao Tu is an U.S.P.H.S. Trainee in Metabolism.

* Trade name Orinase.

** Trade name Diabenese.

TABLE 1

COMPARISON OF DIET ALONE AND INSULIN TO ORAL HYPOGLYCEMIA THERAPY AS SHOWN BY THE FASTING BLOOD SUGAR

Diet Alone	*Tol-buta-mide*	*Chlor-propa-mide*	*Meta-hexa-mide*	*DBI*
Change—mg. per cent	-80.5	-85.0	-83.7	
Superior—No. cases	12	11	13	
Same—No. cases ...	0	1	0	
Inferior—No. cases .	1	1	0	
Insulin				
Change—mg. per cent	+10.9	-16.3	- 6.4	-19.7
Superior—No. cases	8	7	7	8(5)*
Same—No. cases ...	0	1	0	0(2)
Inferior—No. cases .	5	5	5	2(1)

* Figures in parenthesis represent combined DBI and insulin therapy.

produce hypoglycemia in either normal or diabetic individuals. DBI, on the other hand does not produce hypoglycemia in normal individuals but only lowers an abnormally elevated blood sugar.[6]

What Dosage Schedules Should Be Followed

In the case of the sulfa drugs the dosage schedule should include a loading dose which is given to attain an effective blood level and then a daily maintenance dose. Dunlap *et al* have recommended that the maintenance dose be given twice daily in the case of tolbutamide so that nocturnal hyperglycemia will be avoided. A single dose each day is probably adequate for the other drugs. The doses used in this series were as follows:

Drug	*Loading (gm.)*	*Maintenance (gm.)*
Tolbutamide ..	5.0	1.0 -1.5
Chlorpropamide	0.750	0.250
Metahexamide .	0.300	0.050-0.100

For patients who are already on insulin, the insulin may be omitted and the loading dose started the same day.

The approach to treatment with DBI is different since there is no delay in excretion. For patients who are not on insulin in this series the DBI was started as one tablet (.025 gm.) three times per day. This was increased until an effect was noted or until toxic symptoms appeared. For patients who were already on insulin, the drugs were started at 25 mg. per day and increased by 25 mg. until an effect was noted. Whenever evidence of hypoglycemia was noted, then the dose of insulin was decreased. This increase in DBI and decrease in insulin was continued until the minimum dose of insulin could be given. Although the DBI itself will not produce hypoglycemia, the combination with insulin may do so.

What Is to Be Expected in the Patients

In Table 1 are shown the average responses of the fasting blood sugar in patients for each of the sulfa drugs compared to the fasting levels no drug or insulin therapy. There can be no doubt that these compounds justify the name of hypoglycemic drugs. The criteria for a clinical response must include more than just a drop in the blood sugar alone and must take into consideration the amount of glycosuria as well as the ultimate nutrition of the patient. These other factors are included in the overall terms of good, fair, and poor clinical response used here.

Extensive trials in other clinics have reported that 40 to 60 per cent of the patients treated with tolbutamide have shown a satisfactory response.[8-10] This is difficult to evaluate, however, since as shown in Table 2, the response depends on the severity of the diabetes. In this series about half of the mild and moderately severe cases showed a good response and another one-third showed a fair response. In no case classed as severe was there a good or fair response to drug therapy alone. Wildberger and Ricketts, caution, however, that many of the cases are reported in such a way that it is not possible to evaluate the success of the treatment. They reported five carefully selected and controlled patients and by good criteria of treatment found only two of them controlled adequately by tolbutamide.

No striking differences were noted between the different sulfa drugs as regards their clinical effect; although, tolbutamide showed the greatest number of clinical failures and chlorpropamide showed the greatest number of successes with metahexamide in-

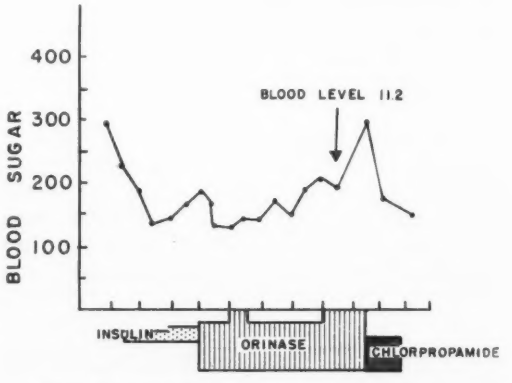

Figure 2. Response of diabetic patient to tolbutamide with secondary failure and then response to chlorpropamide.

termediate between them. It is difficult to compare DBI because of the different circumstances under which it was used.

In 26 Cases

In 26 cases more than one drug was used so that it was possible to compare the results in the same patient. In general there was not much difference between the sulfa drugs such that when one of these was ineffective, the others were also. Some exceptions did appear, however, where chlorpropamide and metahexamide were effective while tolbutamide was not. In four instances there was an initial response to tolbutamide followed by a gradually developing refractoriness, but two of these patients were responsive then to chlorpropamide *(Figure 2)*. One patient was initially responsive to chlorpropamide and finally became unresponsive to this and the other drugs. This secondary failure of the drug appearing after an initial success, is noted usually from six to 12 months after treatment has been started. Several possibilities exist as explanations for this secondary failure among which is the ultimate exhaustion of the beta cells of the pancreas due to excessive stimulation.[12] Evidence against this is the fact that subsequent resumption of insulin dosage shows no increase in the requirement. Another possibility is that there is a decreasing blood level of the drug due to changes in absorption, or more likely in the case of tolbutamide, in the timing of the drug.[7] When such a situation appears the loading dose should be repeated and if no response occurs then treatment with one of the other types of hypoglycemic agent should be tried. The possibility of intercurrent illness should also be entertained since most responsive patients become unresponsive when stress of another type appears in the form of an infection, a fracture, or surgical procedure.

TABLE 2

Degree of Control	*Tolbutamide*	*Chlorpropamide*	*Metahexamide*	*DBI*
Good	10(43)	10(56)	12(53)	5(25)
Severe ..	0(0)	0(0)	0(0)	1(5)*
Moderate	4(16)	4(24)	4(16)	1(5)
Mild ...	6(24)	6(33)	8(32)	3(15)
Obese ..	3	4	7	2
Fair	8(35)	6(33)	7(30)	7(35)
Severe ..	0(0)	0(0)	0(0)	1(5)*
Moderate	2(11)	2(11)	1(3)	3(15)
Mild ...	6(24)	4(22)	6(24)	3(15)
Obese ..	6	4	4	4
Poor	5(22)	2(11)	4(17)	8(40)
Severe ..	2(11)	1(5)	0(0)	3(15)*
Moderate	1(3)	0(0)	2(11)	3(15)
Mild ...	2(11)	1(5)	3(14)	2(10)
Obese ..	2	1	3	5

* In combination with insulin.

TABLE 3

EFFECT OF DURATION OF DIABETES ON RESPONSE TO TREATMENT (AVERAGE YEARS)

	Tolbutamide	*Chlorpropamide*	*Metahexamide*	*DBI*
Good ...	6.1	8.3	6.5	4.8
Fair	3.8	7.0	6.8	7.5
Poor	9.6	2.0	8.6	10.2

Mirsky *et al* reported that early onset of diabetes and long duration of the disease attenuated the successful results with these drugs. In this series, it can be seen *(Table 3)* that the duration of the diabetes was not a very important factor in determining the response to the sulfa drugs, while with DBI a long duration for the disease definitely decreased the chances for a good result. One case here had had diabetes for 25 years, requiring insulin, but had a good response to chlorpropamide.

In Table 3 are seen the successes and failures according to the age of the patient where it is noted that the greatest number of successes appeared in patients over 45 and the greatest number of failures under this age, although there are a significant number of exceptions both ways such that age itself should not be considered a categorical contra-indication to treatment.

Patients who showed a tendency to ketosis were uniformly resistant to the sulfa drugs.[10]

One would hope that the hypoglycemic drugs would offer some unique help in certain problem types of diabetics. One such type of patient is the obese diabetic who has always evaded our efforts at good control with insulin by simply gaining more weight and requiring increasing doses of insulin to maintain control. Reference to Table 2 however shows a random sprinkling of obese persons in each category with a sizable number of obese persons in the poor response group. If drug therapy offers any advantage in this group of patients it is that the drugs do not stimulate the appetite to the same extent as insulin, however, weight loss under drug therapy did not occur to a significant degree. It is suggested that early initial control of some of these patients may be due simply to the fact that they stick to a diet more consistently in order to "prove" to the doctor that the tablet is effective. In all of these cases, however, when eating is resumed and the

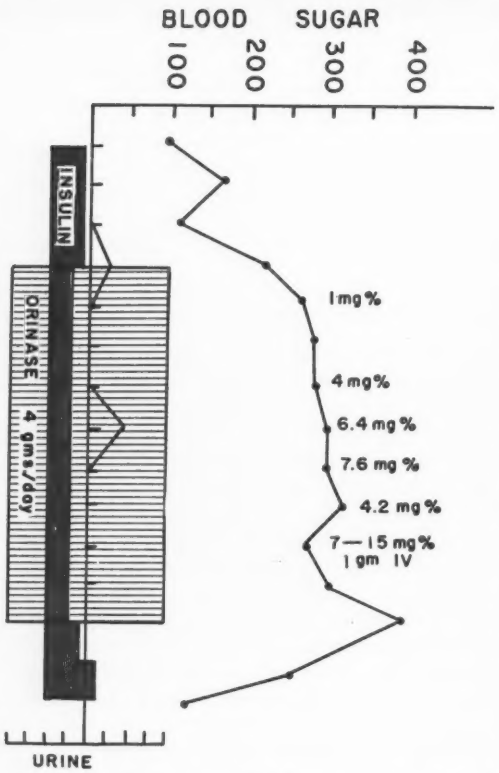

Figure 3. Response showing failure to combination of insulin plus tolbutamide.

weight increases, then lack of control by the drug appears.[9] These drugs then are no substitute to proper dieting in the obese diabetic.

What Relation Do These Drugs Have To Insulin Therapy

Combinations of sulfa drugs with insulin have been recommended as a means of reducing insulin dosage and attaining some stabilization.[14] In our experience one of two effects can be expected from the combination, namely that the sensitivity of the patient to insulin increases such that he becomes more brittle, or there is no effect at all *(Figure 3)*. In three cases in this series violent insulin reactions occurred when the drug was combined with insulin, even though the patients were refractory to the sulfa drug alone.

There is much more to be said for combinations of insulin with DBI,[15] probably because of the lesser tendency of the latter to produce hypoglycemia. Two medicines instead of one for a patient only increase his expense and complicate his care, so when a combination of insulin with DBI is to be used there should be good reason for this. The prime indication for adding DBI to insulin therapy is then the brittle diabetic who cannot be controlled on insulin alone without alternating insulin reactions and ketosis. In this series, the combination has been used in eight cases with the following responses:

Poor	6
Fair	1
Good	1

Both of the successful responses were in labile young diabetics with poor regulation in the face of high insulin doses *(Figure 4)*. In one of these patients the glycosuria was reduced from 300 grams per day to 50 grams per day on the same dose of insulin. Juvenile type diabetics tend to show extreme lability or brittleness at two times in their life: first, during the growth period, and secondly, ten to 20 years later when they begin to develop the late renal complications of diabetes. It is in the first group that the combination of insulin and DBI has been most effective in our hands while all of the failure occurred in the latter group. Baldwin states that children who have hyperglycemia during the day are particularly good candidates for the combination therapy. Although, the insulin dosage may be reduced by this combination, the juvenile diabetic still sustains the same susceptibility to acidosis and if this combination intervenes then full dependence must be placed on insulin alone for its correction. None of the hypoglycemic drugs have any place in the treatment of diabetic ketosis and acidosis.

A comparison of the effectiveness of drug therapy as compared with insulin as measured by the average fasting blood sugar levels is shown in Table 1. As can be seen, in the case of the sulfa drugs, the cases are about evenly split between a superiority of the

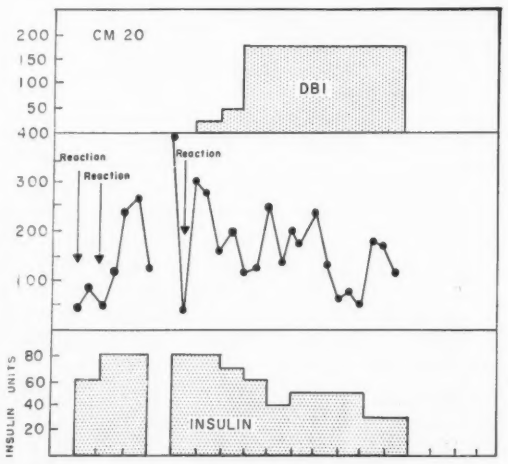

Figure 4. Combination of insulin plus DBI showing "leveling" effect of DBI with disappearance of insulin reactions and reduced insulin dosage.

drug over insulin and an inferiority of the drug to insulin management.

Consistent with the findings of others[17] in all patients taking over 20 units of insulin per day, except for two (one taking 30, one taking 40 units) treatment with sulfa drugs was a failure.

What Untoward Effects May Be Expected

The sulfa drugs may have toxic reactions involving the bone marrow, liver, and skin. In this series no toxic reactions were encountered with tolbutamide. One case developed a severe exfoliative dermatitis while on treatment with chlorpropamide. No clinical toxicity was noted with metahexamide but laboratory studies showed abnormal thymol turbidity and cephalin flocculation tests in five cases and a reduced platelet and neutrophil count in one case. These were all self limited when the drug was stopped.

Hypoglycemic reactions may occur either with or without insulin after administration of the sulfas.[34, 35] In this series there were two patients showing severe hypoglycemia and one showing a mild hypoglycemia after tolbutamide alone. These hypoglycemias were characterized by the fact that they lasted several days and one of these cases developed a permanent encephalopathy. Both of the cases showed impaired renal function before treatment so this should be an indication for particular caution against this complication *(Figure 5)*. Hypoglycemia may also occur in patients apparently refractory to the sulfa drug at the time that insulin therapy is resumed after a drug failure. When such a hypoglycemia appears, intravenous glucose should be maintained for several days.

No serious toxic reactions were noted with DBI. The main difficulty in the use of this drug is nausea which appeared in one of our cases at 25 mg. per day, but usually does not become evident until doses of over 100 mg. per day are used. About 40 per cent of the patients will show nausea above this dose and all will show it if the dose is raised high enough. When nausea appears it usually persists until the dose is reduced.

TABLE 4

EFFECT OF AGE ON RESPONSE TO TREATMENT*

Success	*Tolbutamide*	*Chlorpropamide*	*Metahexamide*	*DBI*
Over 45 .	15(23)	16(25)	15(23)	8(12)
Under 45	3(15)	2(10)	2(10)	4(20)
Failure				
Over 45 .	3(4)	1(2)	2(3)	5(8)
Under 45	2(10)	1(5)	1(5)	5(25)

* Figures indicate number of patients while figures in parenthesis indicate the per cent of the particular age group represented.

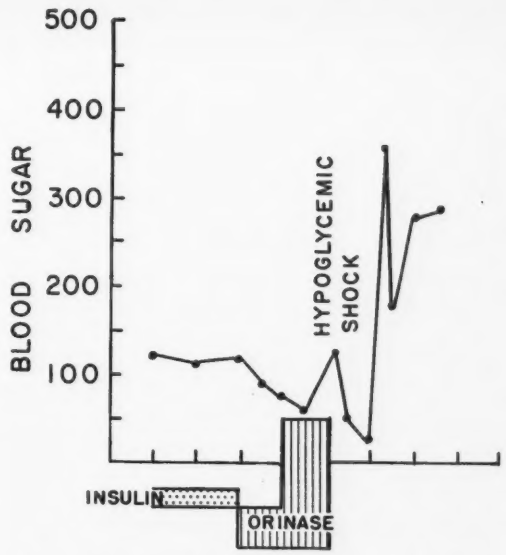

Figure 5. Severe hypoglycemic response to tolbutamide lasting three days.

What Laboratory Controls Are Needed

The laboratory controls which may be considered, fall into three groups: those necessary for following the diabetes, those necessary for detecting toxicity, and those necessary for following the level of the drug in the body. In the first category with sulfa drug treatment the status of the diabetes must be followed quite closely early, since the two great dangers, namely, hypoglycemia or, more commonly, lack of response with the development of acidosis, must be detected early. In this series patients were instructed in the use of urine testing for both acetone and sugar, and were told that if acetone appeared they were to contact the physician immediately and usually the treatment was stopped and insulin reinstituted. As mentioned above even an unresponsive patient may develop serious hypoglycemia when insulin is reinstituted so the patient is instructed to start back on half the former dose and increase each day back to the original dose at four days. A certain amount of glycosuria can be tolerated during the change over period. Toxicity determinations *i.e.*, blood counts and liver function tests are not rigorously indicated with tolbutamide but should probably be checked occasionally with chlorpropamide and certainly with metahexamide.

Methods for following the blood level of the drug are available but not readily adaptable to hospital

laboratories. Measurements of the blood level are usually not indicated in the routine cases. Effective blood levels for tolbutamide and chlorpropamide are between 8 and 20 mg. per cent while for metahexamide the level is between 1-3 mg. per cent. With DBI no particular control other than control of the diabetes is indicated in the routine case.

How Do the Drugs Work

A great wealth of conflicting experimental work exists directed towards a solution of this problem. The early ideas that there is a change produced by the sulfonylureas in the alpha cells of the pancreas has not been substantiated. The sulfa drugs decreased the beta granules in the islets under acute conditions but in chronic administration no changes were noted.[18-20] For the sulfa drugs to be effective as hypoglycemic agents, most of the evidence indicates that pancreatic insulin production must be present and it is in diabetics of the type where Wrenshall and Best[21] found extractable insulin in the pancreas and Goren *et al*[22] found insulin in the plasma, that these drugs are effective.

Tolbutamide, under some circumstances, causes a maximal effect when it is injected into the pancreatic artery. Evidence against the theory, however, that the hypoglycemic effect is due to the insulin secreted under this stimulation is that insulin alone causes a rise in the blood pyruvate while tolbutamide causes a fall.[23, 24] Some workers have thought that this difference could be explained on the basis of route of administration but Galansino *et al*[24] could find no difference on this basis. Much evidence exists to the effect that the sulfa drugs may lower the blood sugar by decreasing hepatic glucose production.[25-29] There is no evidence that the sulfa drugs have any effect on the peripheral tissues. Mirsky[30] has shown that the sulfa drugs are "insulinase" inhibitors *in vitro*. Bolinger and Grady[31] showed that the disappearance of labeled insulin from the plasma was accelerated after tolbutamide.

The site of action of DBI is different from that of the sulfas in that there is a demonstrable effect on the peripheral tissues. Clarke and Forbath[32] and Bolinger *et al*[33, 34] demonstrated that DBI increases the glucose uptake of the rat diaphragm. This differs from the similar effect of insulin on this tissue in that the tissue glycogen and potassium are depleted by DBI. Groen *et al*[35] demonstrated that insulin effect on skeletal muscle is easily blocked by small amounts of adrenalin and Bolinger *et al* [33] have shown that DBI effect is not nearly so sensitive to this block. Some of the clinical benefit of DBI may conceivably be due to this partial blocking of adrenalin effects on the peripheral tissues.

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Psychiatry Today

(Continued from page 134)

trated in urban areas. Attention has previously been called to the probability that more psychiatric wards will be created in general hospitals and the fact that new medications make it practical to treat more patients on an out-patient basis. Accordingly, it should be reasonable to assume that the general practitioner will be treating more psychiatric cases and that the efforts now in progress to attract psychiatrists to the smaller communities will be increased. Private psychiatric practice in the smaller communities should be more practical than it has been in the past. It may be possible in some communities to combine private practice with part-time service in a community clinic for lower income patients. Most community clinics use a team approach and bring with them the skills of the psychologist and the social worker, as well as the physician. Because of the shortage of psychiatrists, efforts have been made to expand many residency training programs. At the present time at the University of Kansas Medical Center there are six residents in psychiatry and it is expected soon to increase the number to twelve.

At the national level one step has been taken to add to the supply of psychiatrists. The Public Health Service has established a system of grants for psychiatric training for general practitioners who wish to specialize in this field. These provide adequate stipends to support a person several years out of school. The physician interested in such a program must first be accepted by an approved training center which then applies for the grant. For the general practitioner who wishes to increase his skill in psychiatric techniques but who does not wish to specialize in psychiatry, we must anticipate further expansion of post-graduate programs.

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More Examinations Helpful

Periodic examinations rank as an increasingly important contribution to occupational health, according to the current issue of *Patterns of Disease*, prepared by Parke, Davis & Company for the medical profession.

Their role is underscored by the fact that in spite of variations in examinations, at least 15 per cent and as many as 40 per cent of persons examined are found to have a significant disease or defect previously unknown. Moreover, half or more of these conditions are asymptomatic when discovered.

Recommended tests include: complete blood cell count with hematocrit, erythrocyte sedimentation rate, urinalysis, serology, stool examination for parasites and occult blood, chest x-ray, and electrocardiogram.

Proctosigmoidoscopic examination should probably be included in usual examination procedures and, for women, pelvic examination, and cervical smear study is recommended.

Renal Angiography

Records Information About the Renal Arterial System

COLVIN H. AGNEW, M.D., *Kansas City*

RENAL ANGIOGRAPHY FURNISHES precise information about the renal arterial system. It may be performed by direct puncture (usually accidental) and by catheter technique (usually deliberate). In the early 1950's several investigators employed polyethylene or cardiac catheters (Helmsworth, *et al,* Bierman and associates, Pierce, Goodwin, Hooks, and others). This method never received widespread American acceptance, but the availability of radiopaque polyethylene catheters has revived interest in the method.

Translumbar aortography has been used extensively in the investigation of renal vessels; however, there is some disagreement (Evans and Nesbitt) as to its value. Nesbitt emphasizes the need for careful selection of patients with hypertension for angiography. Gregg believes that selective angiography is the best approach to renal arteriography. Intravenous techniques have been used for 20 years to visualize renal arteries (Robb and Sternberg). Recent refinements in this technique includes the employment of radioactive I-131 tracers (Porporis and others) to time exposure, and bilateral venous injections. This method has the advantage of being somewhat less hazardous; however many of these aortograms lack renal detail.

Method

Seldinger's technique for percutaneous catheter insertion has been given careful consideration; however, I favor exposure of the artery as developed by Derrick and associates, because it permits control of hemorrhage, even though it is more time consuming. The time saved may not be to the patient's advantage if it is at the expense of local complications. The fasting, premedicated patient is placed upon a radiolucent mattress. (General anesthesia is recommended for children.) Under local anesthesia the femoral artery is exposed. The adventitia is stripped, umbilical tapes are looped above and below the site for the insertion of the catheter. The distal femoral artery is injected with 5 ml. of 0.02 per cent solution of heparin. Some favor heparinization of the patient. A short transverse incision is made in the artery and the radiopaque polyethylene catheter (KIFA) with the proper shape is inserted into the femoral artery. A stainless steel stylet almost straightens the catheter before its insertion. The catheter is advanced to the approximate level of the renal arteries, the stylet removed, and fluoroscopy is employed for final positioning, 6 ml. of Renografin 60 per cent or Hypaque 50 per cent contrast material is entirely adequate for complete visualization. Serial filming is desirable. Image amplification may be extremely useful. Until now our experience has been acquired with the usual fluoroscopic equipment. It is our intention to record the information by cine-technique in the future.

Hypertension is curable by corrective arterial surgery or nephrectomy in selected patients. Renal angiography offers a method of selecting the proper treatment and precisely locating the lesion. The method, results, advantages, and disadvantages are summarized.

Two Advantages

The radiopaque catheter has two significant advantages: (1) it may be easily seen and (2) a tip may be moulded for the specific application. To direct the tip toward the ipsilateral artery there must be a gradual curve in the body of the catheter. To enter the contralateral artery the body of the catheter must have an S-shaped bend. It is usually easy to distinguish entry in a renal artery from entry in a lumbar artery. For injection, however, the tip should not be in the renal artery but only at the orifice, thus avoiding unnecessary renal artery spasm. It is conceivable that the catheter might pass an atheromatous plaque and the arteriogram would then show no abnormality. Our experience has largely been with a single end-hole catheter. It is entirely possible however, that some arrangement of punched side-holes and an open end-hole will be superior, and that is now under investigation.

Results

The most striking feature of this method has been the excellent anatomic detail. It has been surprisingly

From the Department of Radiology, University of Kansas Medical Center, Kansas City, Kansas.

The cooperation of R. N. Cooley, M.D., and J. R. Derrick, M.D., University of Texas Medical Branch, Galveston, Texas, is gratefully acknowledged.

easy to place a catheter in either renal artery if the catheter has had the proper bend. We have previously published the appearance of a narrow stenotic band with a post-stenotic dilatation demonstrated by translumbar aortography and proved to be a congenital stenosis.[1] The patient had a vascular repair with a temporary relief of hypertension. With the recurrence of hypertension an aortogram demonstrated that the end-to-end anastomosis was of insufficient caliber and a nephrectomy was done with relief of the hypertension. In the same article we published an arteriogram of the vascular pattern in a man with essential hypertension showing a normal caliber renal artery, although somewhat scalloped, and the absence of interlobular branches. The patient died of a fulminating essential hypertension about three months later. Our third case was a child with hypertension who had an unsuccessful lumbar aortogram approximately nine months earlier followed by a successful selective catheterization bilaterally *(Figure 1-C)*. The boy's left arteriogram was distinctly normal. On the right there was a stenotic area with a poststenotic dilatation at the origin of the major branch to the right upper pole. The hypertension has apparently been cured by resection and end-to-end anastomosis. A second child was investigated by this method and no renal artery was demonstrated on the left. Two patients had their celiac axis investigated, and during this procedure renal angiograms were also made. These normotensive patients demonstrated good filling of the interlobular arteries and uniformity of the caliber of the major vessels. These cases have been investigated at the University of Texas Medical Branch, Galveston. An additional child with hypertension has been investigated here. A preliminary film demonstrated calcification in the region of the left renal artery. Several attempts to insert a catheter failed, and no dye was seen entering the renal artery. It should be mentioned that the pyelogram showed good renal function; however, as pointed out by Squire the execretory pyelogram is not a sensitive reflector of kidney function.

Discussion

While there have been some notable successes in the relief of hypertension following surgery, overenthusiasm may have resulted in improper selection of patients.[2] Advances in surgery through the use of vascular prostheses has widened the scope of surgical attack and refocused attention upon the role of renal ischemia in the production of hypertension. Morris and associates before the Southern Society for Clinical Research recently reported on the experiences in 30 patients with hypertension subjected to this treatment. Twenty-eight were essentially relieved of their hypertension. Defective blood supply due to atherosclerotic plaques, congenital stenosis, aberrant arteries, and renal artery aneurysms have been demonstrated to be a cause of hypertension in humans. It might be worthwhile to review the renal ischemia hypothesis in the production of renal hypertension. The kidney produces a substance (renin) which combines with the plasma globulin (hypertensinogen) to produce a substance (angiotonin) which will

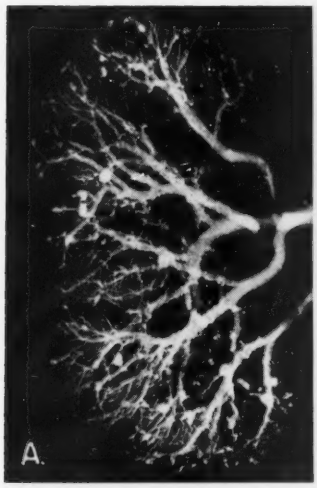

Figure 1-A. Angiogram from a patient with polyarteritis nodosum. This was obtained at autopsy by Meaney and associates (reproduced through the courtesy of *Cleveland Clinic Quarterly)*, and shows not only the fine detail possible but the microaneurysms seen in this disease.

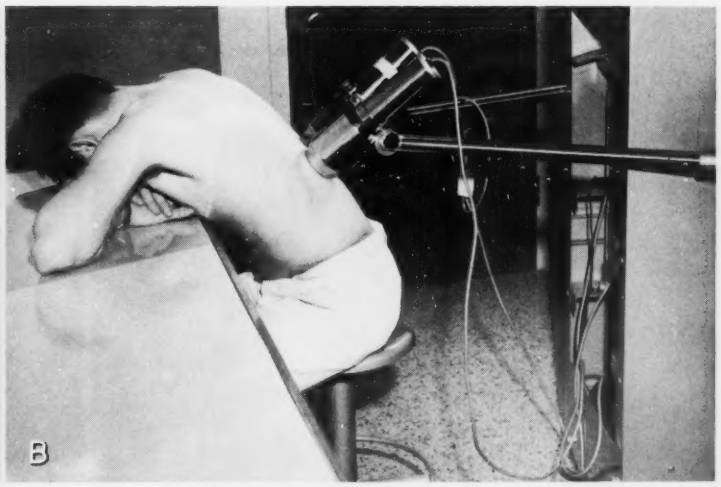

Figure 1-B. The patient in a flexed sitting position with the narrow beam collimator probes almost touching the skin. In practice, the probes are inclined sharply downward. This position must be maintained about 15 minutes for a differential renal study.

elevate blood pressure. Huggins has shown that there is also extrarenal formation of vasopressor substances. It appears that if surgery is undertaken within a reasonable period (perhaps three years) after the onset of hypertension, success may follow. On the other hand if the hypertension becomes fixed, there is not a sustained relief from hypertension in spite of the corrective operative procedure. Angiograms of kidneys from hypertensive patients show a distinctive radiographic appearance—sparse or absent filling of the interlobular arteries (Meaney, *et al*). Differential renal clearance tests play an important role in the investigation of hypertension.[16] We are just beginning to employ external counting of radioactive Diodrast I-131 *(Figure 1-B)*. Distinctive tracings have been found in normally and abnormally functioning kidneys.[7] We anticipate that it will augment preangiographic work-up.

Application

1. Renal Tumors: While the distinction between renal cyst and neoplasm can usually be made by angiography, surgery will be resorted to regardless of the angiograms in the majority of cases. It is not, therefore, recommended unless it will be decisive in the management.

2. Renal Tuberculosis: I have no personal experience. European authors (Frimann-Dahl and Gregg and associates) have found it of value since segmental nephrectomy has a role in the surgical management.

3. Miscellaneous Conditions: (a) Hydronephrosis, (b) polycystic disease, (c) hypoplastic kidney, (d) renal infarcts, and (e) horseshoe kidney are susceptible to diagnosis based upon their sufficiently characteristic vascular pattern. These conditions may be confirmed by simpler procedures.

4. Hypertension: It would appear that angiography of the kidneys has its principal value in the investigation of hypertension. Poutasse advocates that hypertensive patients, regardless of age or duration of disease, who show a disparity in size by intravenous pyelography should be studied by angiography. Unexplained hypertension in childhood should be studied by angiography. In older persons an accelerated development of hypertension may justify renal angiography. Judicious employment of the method will reduce the number of unnecessary procedures.

Comment

The advantages of selective renal angiography may be summarized as follows:

1. Precise demonstration of the renal artery and kidney. **2.** Minimal visualization of irrelevant areas. **3.** Eliminate intramural injection of contrast substance. **4.** Reduce the amount of contrast substance. **5.** Permits unrestricted positioning of the patient. **6.** Reduces the requirement for analgesia.

The disadvantages may be summarized as follows: **1.** Requires more time. **2.** May not be successful in tortuous vessels. **3.** May enter the wrong vessel. **4.** Danger of reaction to the catheter. **5.** Increased radiation to the patient and operator. **6.** Should employ serial filming. **7.** May overlook aberrant arteries. This may be minimized by injecting the aorta before the catheter is withdrawn with sufficient contrast to fill any other remote vessels.

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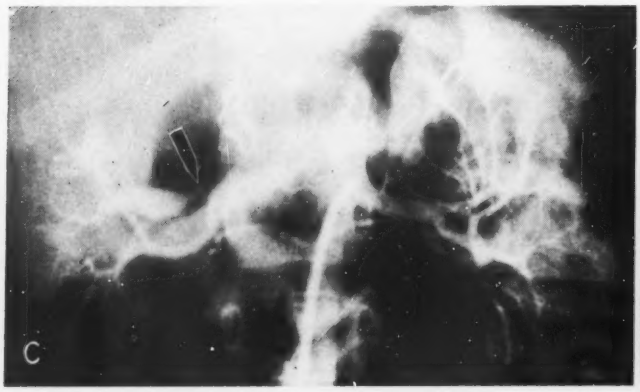

Figure 1-C. Angiograms of a boy with hypertension. The catheter is near the left renal orifice. This is a normal left renal angiogram. The arrow points to a narrowed area in the branch to the right upper pole with postenotic dilatation.

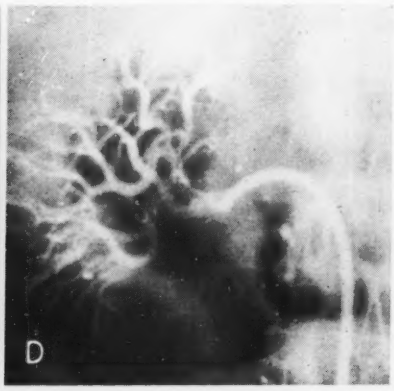

Figure 1-D. A right renal angiogram in a normotensive person. Three ml. adequately fill this kidney. The catheter should be at the orifice of the renal artery at the time of injection.

Isotope Chromium^{51}

The Evaluation of Selected Anemias With Radioactive Material

JOHN H. WINEINGER, M.D.;* SLOAN J. WILSON, M.D.;† *and* WILLIAM E. LARSEN, M.D., *Kansas City***

RADIOACTIVE CHROMIUM (Cr^{51}) is extremely useful for tagging red cells. Once the tagged red cell is destroyed by the body, the Cr^{51} is excreted in the urine and is not metabolically utilized. These characteristics are valuable in determining blood volume, red cell survival in normal subjects and suspected hemolytic disorders, and the sites of red cell sequestration.[1-11]

The usual laboratory tests for hemolysis are of an indirect nature and may not indicate blood destruction. The tagging of red cells gives more exact information as to destruction. Two methods may be

The destruction of red cells and their sequestration in the spleen and liver is demonstrated by use of red cells tagged with the radioactive isotope Cr.^{51}

From the Section of Hematology, Department of Medicine, University of Kansas School of Medicine, Kansas City, Kansas.

*Former Fellow in Hematology, University of Kansas Medical Center, Tucson, Arizona.

† Associate Professor of Medicine and Head of the Section of Hematology, University of Kansas School of Medicine.

** Assistant Professor of Medicine, University of Kansas School of Medicine.

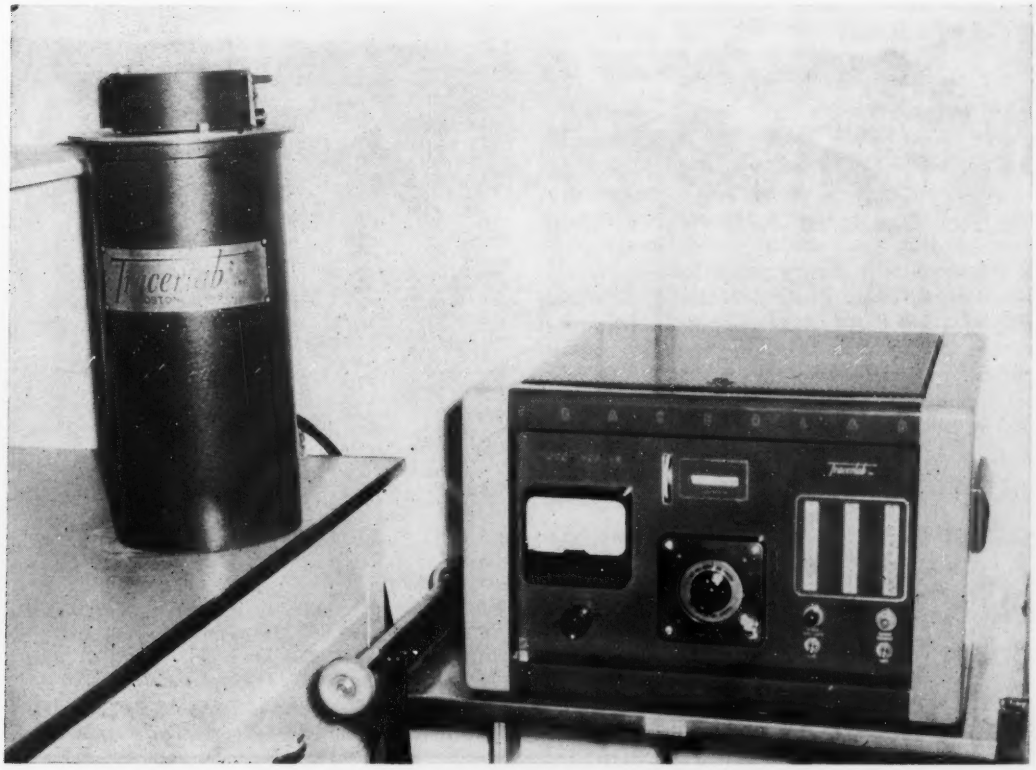

Figure 1. Well-type scintillation counter and a scaler used in recording radioactivity of Cr^{51}-tagged red cells.

used: (1) The tagging of a patient's own cells, and (2) the tagging of normal donor cells and observing the rate of destruction in the patient.

Cell Rate Destruction

By observing the rate of destruction and the sites of sequestration, it may be possible to predict response to splenectomy. The important consideration is to demonstrate that the spleen is the site of active red cell sequestration. If the red cell survival is shortened and the spleen is the site of sequestration, splenectomy is recommended.

In the present study, the red cell survival was observed in 20 selected patients, 18 of whom had either moderate or severe anemia (see *Table I*). The results were compared with tests usually available to determine hemolysis. An example of body scanning is presented to determine the sites of red cell sequestration and to evaluate the data in predicting the effect of splenectomy.

TABLE I
TABULATION OF OBSERVATIONS IN PATIENTS*

Case	Diagnosis	Sex	Age	Hb. Gm.	Retic. Per Cent	Bilirubin DIR.	Bilirubin TOT.	24 Hr. U. U.	Iron Serum	Bone Marrow	Cr^{51} 50 Per Cent Survival
1 A. H.	A.H.A.	M	62	8.0	0.8	0.6	2.3	22	220	Marked Erythroid Hyperplasia	17 days
2 A. C.	A.H.A.	F	52	2.9	87.8	0.5	3.9	18.1	182	Marked Erythroid Hyperplasia	2.2 days
3 C. S.	A.H.A.	M	57	4.8	36.4	0.4	4.2	13.5	220	Marked Erythroid Hyperplasia	40 hrs.
4 J. B.	A.H.A.	M	60	11.2	41.4	0.6	3.2	5.3	115	Marked Erythroid Hyperplasia	3.0 days
5. R. P.	A.H.A.	M	61	7.8	13.0	0.9	3.2	32.3	125	Marked Erythroid Hyperplasia	5.5 days
6 O. B.	Myeloid Metaplasia	M	62	9.7	1.4	0.1	0.9		75	Myeloid Metaplasia	25 days
7 L. N.	Myeloid Metaplasia	F	71	7.5	2.0				51		24 days
8 L. H.	Acute Monocytic Leukemia	M	54	8.4	3.0	0.1	0.4	0.3 (2 hr.)		Increased Immature Monos.	20 days
9 F. S.	C.L.L. and Hepatitis	F	40	7.8	8.0	12.0	14.0	17	200	C.L.L. and Erythroid Hyperplasia	12.5 days
10 C. K.	Hodgkin's Disease	F	59	7.2	0.0	0.0	0.5	2.8	20	Myeloid and Megakaryocytic Hyperplasia	15 days
11 R. G.	C.L.L.	M	49	9.2	5.6	0.1	0.3	2.5		C.L.L.	20 days
12 S. G.	T.B. and Anemia	F	69	8.3	0.2	0.1	0.7	8.0		Erythroid Hyperplasia	18.6 days
13 E. M.	Macrocytic	F	76	9.0	8.5	0.2	1.3			Marked Erythroid Hyperplasia	14 days
14 J. E.	Iron Def. Anemia	M	25	8.5	3.0	0.1	0.2	6.6	18	Erythroid Hyperplasia No Iron	26 days
15 R. S.	Pancytopenia	M	15	6.0	6.8	0.16	1.1	10.8		Erythroid Hyperplasia	31 days
16 V. M. E.	S.L.E.	F	18	10.0	2.8	0.3	0.7		30	Increased Eos. Lymphs and Plasma Cells	30 days
17 J. D.	Anemia and Diabetes	M	68	8.4		0.1	1.3		175	Erythroid Hyperplasia	27.5 days
18 H. K.	Hemochromatosis	M	67	11.5	3.2	0.4	0.9	0.2 (2 hr.)	100	Erythroid Hyperplasia	23 days
19 H. L.	Normal	M	40	14.2	0.4	0.1	0.7	4.06	30		31 days
20 T. F.	Normal	F	46	13.0	1.2	0.2	0.7		30		29 days

* The results of the Cr^{51}-tagged red cell survival studies may be compared with the more commonly used indirect tests for determining whether or not a patient is hemolyzing red cells.

Methods

All red cell labeling was performed under sterile conditions with sodium chromate ($Na_2Cr^{51}O_2$) diluted with normal saline to a specific activity of 100 microcuries per cc. as of time of assay. One hundred microcuries were added to 15 cc. of acid-citrate-dextrose solution. To this mixture was added 30 to 40 cc. of whole blood, with constant agitation. Thirty minutes with frequent mixing were allowed for the tagging of the red cells. At the end of this period of time, 100 Mg. of ascorbic acid were added to the mixture to stop any further labeling of the red cells by the chromate. This mixture was then reinjected into the patient. After one hour, a sample of blood was drawn from the patient and placed in dry "balanced" oxalate (potassium ammonium oxalate) to be used as a standard. The standard was prepared by taking duplicate 2-cc. aliquots of this first blood sample. They were centrifuged at 3,000 rpm. for two minutes. Plasma was removed and the volume was reconstituted to 2 cc. with distilled water to hemolyze the red cells and, thereby, insure uniform radioactivity.

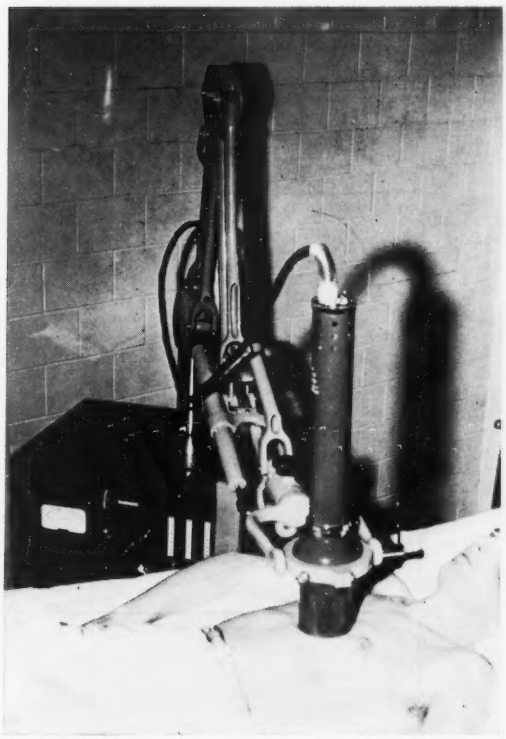

Figure 2. Measurement of body surface activity with a directional scintillation counter. Radioactivity is measured over the precordium, liver, spleen and sacrum. Ultimate sites of red cell sequestration may be determined.

Specimens were then collected from the patient at appropriate intervals in dry "balanced" oxalate. The radioactivity of 2 cc. of whole blood was determined in duplicate and compared with the standard. Correction for background was made. Activity of the patient's blood was expressed according to the formula:

$$\frac{\text{counts per min. of specimen}}{\text{counts per min. of standard}} \times 100 = \text{per cent on given day}$$

Activity of the plasma was also determined for each specimen; but, with the exception of the first day, was found to be of such low order (10 to 30 counts per minute) that it was ignored. The activity of all blood was determined with a well-type scintillation counter, and the Tracerlab 1,000 Scaler was used as a recording device *(Figure 1)*. Normal red cell survival is measured in terms of 50 per cent survival, the normal being from 27 to 31 days.

Body surface activity was determined with a directional scintillation counter, having a conical collimator four inches in depth and three inches in internal diameter at the open end *(Figure 2)*. Radioactivity over the precordium, liver, spleen, and sacrum was determined 30 minutes after injection of the tagged blood. All subsequent determinations were compared with these values to establish degree of organ uptake of radioactivity.

How Areas Are Counted

The areas to be counted were determined by physical examination. The counter was placed in such a way that the crystal was parallel to the body surface.

According to Jandl, *et al.*, an important degree of the activity of any given organ is derived from the profusing blood—as well as from scatter radiation from other organs and nearby vessels. It is impossible to determine absolute amounts of organ activity, since it has been found that precordial activity roughly parallels the activity of the whole blood; the relative expression of activity over a specific organ to activity over the precordium was used as an expression of the function of activity accumulated in the organ concerned.

Observations

In this study, there were five cases of idiopathic acquired hemolytic anemia (see *Table I*, Cases 1, 2, 3, 4, and 5). In our subjects, the destruction of red cells was extremely rapid, with 50 per cent survival ranging from 40 hours to 5.5 days. In the fifth patient the survival was 17 days.

In all but one of the cases of idiopathic acquired hemolytic anemia, the red cell survival studies could be correlated with the more commonly used laboratory procedures. These tests included reticulocyte count, bilirubin, urinary urobilinogen, serum iron,

and bone marrow studies. The results are tabulated in *Table I.*

There was definitely increased destruction of red cells in Cases 8, 9, 10, 11, 12, and 13, the 50 per cent survival being 20 days or less. It will be noted that the survival studies did not always agree with the other observations. The survival studies revealed the cause of the anemia—increased destruction due to hemolysis. Case 13 is of particular interest. This patient had a B_{12} and folic acid resistant megaloblastic anemia. The Co^{60}-B_{12} test of Schilling revealed normal absorption, so the patient did not have pernicious anemia. Red cell survival studies revealed a hemolytic anemia.

In Cases 7 and 8, there was evidence of slight destruction.

Figure 3 illustrates survival curves obtained in a normal subject and in representative patients.

Body scanning was done in a normal subject *(Figure 4)* and in a patient with an acute episode of idiopathic acquired hemolytic anemia (Case 5) *(Figure 5)*. Survival studies were also done. In the normal subject, the survival time was 29 days. Also note that there is little difference in the readings of the scanner over the spleen, liver and sacrum. Compare these findings with those of Case 5. The survival of red cells is drastically shortened and there is increased activity noted over the spleen and liver. All of these observations were repeated with tagged donor cells, the results being the same. The Coombs' test was positive.

On the basis of our observations, it was predicted that a splenectomy would not be curative. Unfortunately, this prediction was correct and the patient did not respond to splenectomy. He later responded to corticosteroids.

Discussion

At times it is impossible to determine the absolute cause of anemia. It is now possible to determine the rate of destruction of red cells and the site of sequestration. Thus, this additional knowledge has made it obvious that many of the unexplained anemias may be of a hemolytic type. Hemolysis has been described in malignancies, cirrhosis of the liver, the nephritides and various types of infections. It would

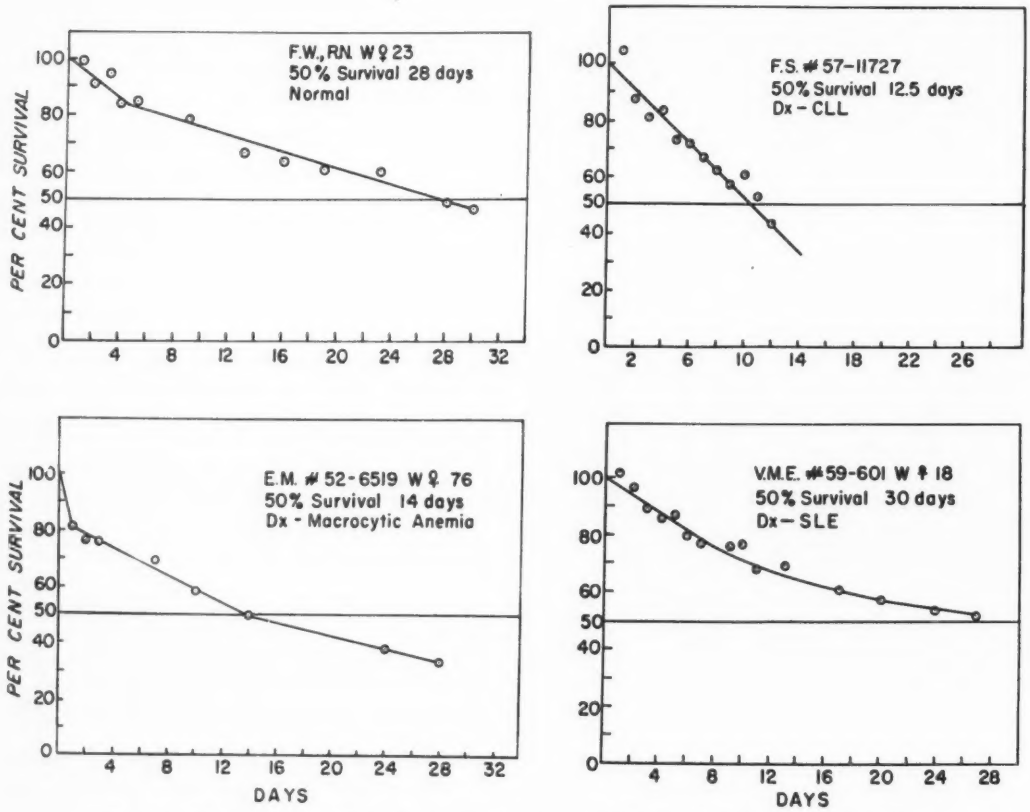

Figure 3. Illustrative red-cell survival curves in a normal subject and representative patients.

seem that an increased destruction of red cells should always be considered in bizarre, unexplained anemia.

It should be emphasized that the commonly used tests to demonstrate hemolysis are, in reality, indirect and may be positive when hemolysis is absent. Fecal urobilinogen studies, in our experience, have been most difficult to collect correctly and determine accurately. The true test, direct in character, is the actual tagging of red cells and the measurement of their survival time.

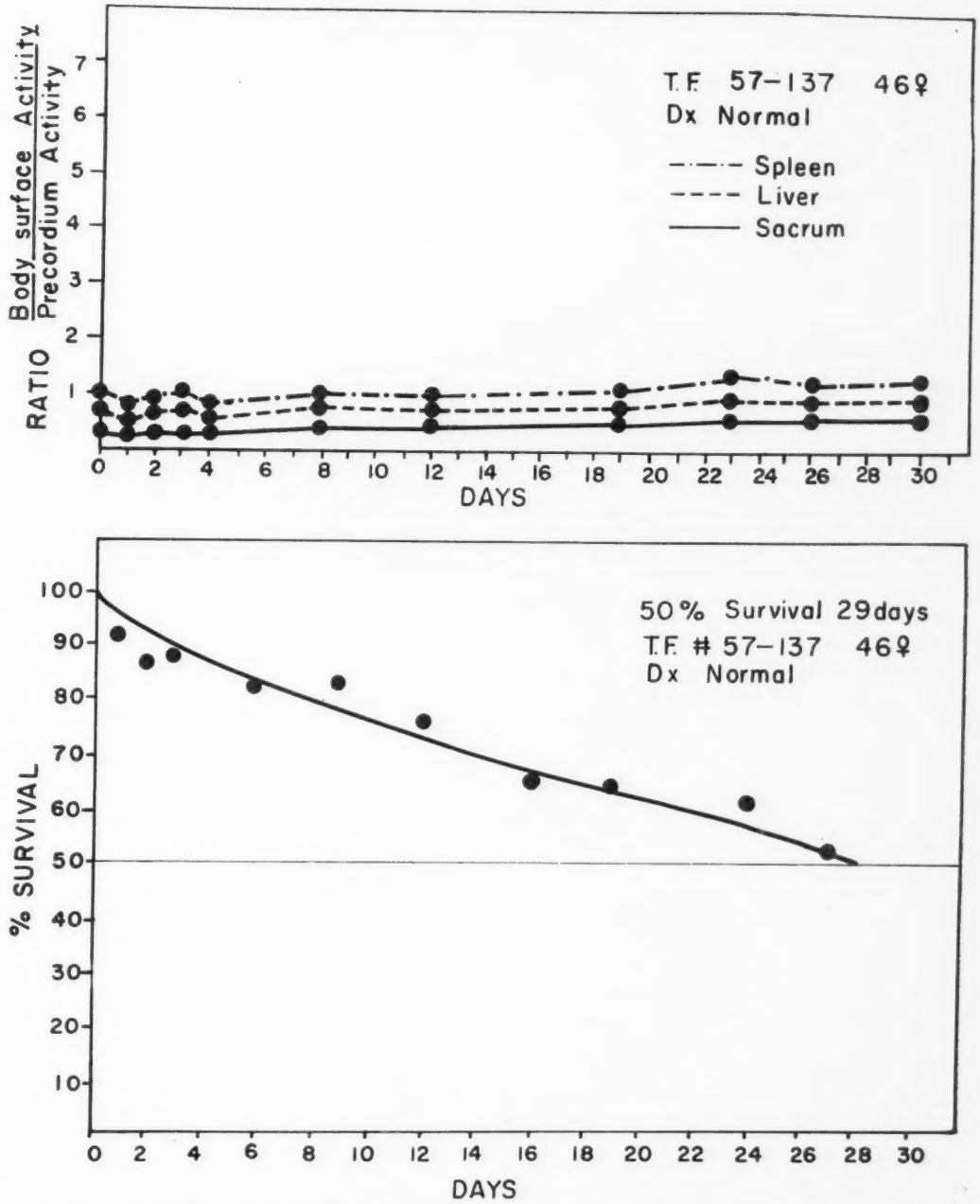

Figure 4. Studies on the survival of Cr^{51}-tagged red cells and body surface activity in a normal subject.

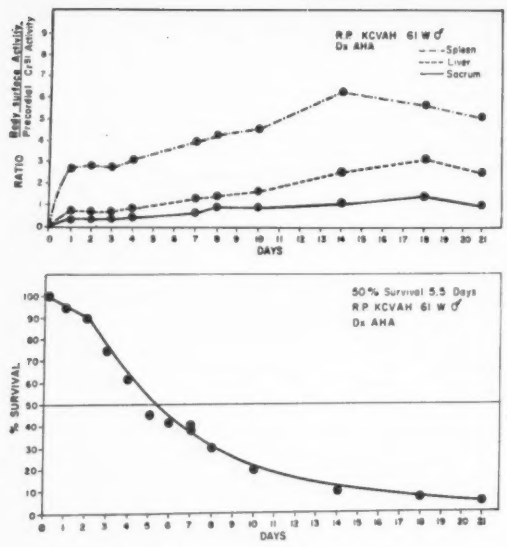

Figure 5. Studies on the survival of Cr^{51}-tagged red cells and body surface scanning in a patient with idiopathic acquired hemolytic anemia. Compare with *Figure 4*. The survival is decreased and the cells sequestered in the liver and spleen.

The use of body surface scanning to determine sites of sequestration has been difficult because many observations were made too soon after the injection of the chromate tagged red cells. It has been pointed out that, if the time for reaching a plateau is prolonged, surgery will be beneficial.[4, 7, 8, 11]

Red cell survival is greatly shortened in some acquired hemolytic anemias. Hemolysis may not be clinically evident in many patients if the destruction rate is only moderately increased. This is best demonstrated by red cell survival studies.

Body scanning may be useful in determining the site of sequestration of red cells. The results of splenectomy can be predicted.

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Hypnotic Wart Treatment

A Report of Treatment of Warts In An Eleven Year Old Child

WILLIAM SEEMAN, Ph.D.,* ***Kansas City***

THE TREATMENT OF WARTS by hypnotic suggestion is not exactly rare; indeed, Sinclair-Gieben and Chalmers in a recent issue of *The Lancet* state that "many workers have described the treatment of warts by hypnotic suggestion." One of the interesting features of the case to be reported here is the noteworthy efficiency (in terms of time) of the treatment; a second interesting feature of the case is the fact that the hypnotic treatment followed the removal of warts by surgery, with a subsequent return of the warts almost immediately.

Etiology of Warts

Concerning the etiology of warts I can do no better than to quote from Sinclair-Gieben and Chalmers: "The cause of warts is not as clear as some people suppose. The common assumption that a virus is responsible is based on the work of Variot (1894) and Ciuffo (1907), but these authors and others have shown only the presence of a virus by inference, inasmuch as they managed to transmit warts by the filtrate of ground-up warts. Inclusion bodies have been demonstrated in certain warts (Lyell 1950), but this in itself cannot be taken as proof of a virus. Pillsbury *et al.* (1956) cite the Koebner phenomenon (i.e., the appearance of lesions at the site of injury) as proof of the infective nature of warts, but this phenomenon is seen in other skin conditions, such as lichen planus and psoriasis, where no infective theory stands up to simple tests."

Case History

The mother of an eleven year old girl of above average intelligence was referred to this department by her pediatrician. Only shortly before the referral the girl had been suffering from several warts on the ball of her left foot. The warts had been surgically removed, only to return almost at once. At this point the surgeon suggested that another kind of treatment might be indicated. Following this, the mother was referred to the department of psychiatry of the Kansas University Medical Center by the pediatrician.

The technique of hypnotic induction used with the little girl was that of an imaginary television viewing. The girl was asked to close her eyes and to visualize her favorite program. (It turned out to be 77 Sunset Strip.) As she concentrated on this imaginary television program she was given suggestions to "relax deeper and deeper" and to go "deeper and deeper into hypnosis." Since the criterion of a sufficiently "deep" hypnotic state for the treatment of warts is said by Sinclair-Gieben and Chalmers to be one in which a post-hypnotic suggestion could be effectively given (which is to say, could be carried out by the hypnotic subject on "waking"), the post-hypnotic suggestion was given to the girl that on "waking," she would find her hand itching. And, indeed, she did indicate that she experienced the itching and did scratch the hand. (This is perhaps the place to point out that operators who have occasion to deal with hypnotic states in children are in general agreement that children typically have no difficulty reaching satisfactory "depth.")

This paper reports a case involving the treatment of warts by hypnosis in an 11 year old girl. The warts disappeared following the third hypnotic treatment. Attention is called to experimental evidence justifying the presumption that the hypnotic treatment was actually the agent responsible for the disappearance of the warts.

How Suggestions Are Placed

In general, the hypnotic sessions were carried out in the following manner: When the girl was considered to be sufficiently "deep" in the hypnotic state she was told: "Your skin has natural healing powers. You will find as time passes that your warts will get smaller and smaller. They will become smaller and smaller and eventually disappear. Now I want you to imagine that I have a salve of some kind. I am going to put this on your foot and cover the warts. You will immediately experience the soothing effects of the salve. Furthermore, this salve is going to speed up the

(Continued on page 156)

* Professor of Psychiatry (Psychology), University of Kansas School of Medicine, Kansas City, Kansas.

Peutz-Jeghers Syndrome

Intestinal Polyposis Associated With Pigmentation

WILLIAM A. REED, M.D., ***Kansas City***

IN RECENT YEARS a disease entity consisting of intestinal polyposis with pigmented spots of the skin and oral mucosa has been recognized and established. Although considered rare before the last decade, a review of the literature reveals approximately 90 recorded cases.

The first reference to this condition was by Hutchinson in 1896 when attention was drawn to the abnormal pigmentation. It remained for Peutz in 1921 to describe the association of abnormal pigmented spots and intestinal polyps, and to suggest that an hereditary factor might be involved. Jeghers, Ravitch, and Bartholomew have published excellent reviews of the disease in recent years.

Three Cases

The present report is concerned with three patients with this disease recently seen at the University of Kansas Medical Center.

Case One

A 40-year-old Negro housewife was admitted to the Medical Center on July 24, 1957. She was in labor on admission and gave birth to normal twins a few hours later. In the immediate post partum period manifestations of mild eclampsia and signs of small bowel obstruction appeared. Conservative treatment was instituted with improvement of the eclampsia, but the bowel obstruction persisted.

The significant facts of the family and past history indicated that a laparotomy had been done ten years previously at another hospital, subsequent to symptoms of bowel obstruction. An uneventful recovery followed the operation but the patient was unable to give an accurate account regarding the findings.

Her mother died at 30 years of age of "stomach trouble." Her father is living and well. One sister, now 38 years of age, had been operated upon for bowel obstruction at 21 years of age and is now living and well. Pigmented spots are present on the lips of the sister. The patient is the mother of nine living children ranging in age from one to 18 years. Pigmented spots are present on four children, two sons and two daughters. The patient was seen in consultation by the surgical service on the seventh post partum day when abdominal distention and cramping pain in the right side of the abdomen were noted. Numerous black smooth pigmented spots were present on the lips, buccal mucosa, and palmar surface of the hands.

The hemoglobin was 12.0 grams; the white blood cell count was 12,450; non-protein nitrogen, 77.5 mgms. per cent; serum sodium, 130 mEq/L; serum potassium, 5.5 mEq/L; chloride, 103 mEq/L; Co_2, 14 mEq/L. Roentgenograms of the abdomen showed multiple loops of dilated small intestine.

A brief review of the literature with a discussion of the salient features of the Peutz-Jeghers Syndrome is presented. Three additional new cases in a single family are described.

Laparotomy was advised and done on July 31, 1957. The cause of obstruction was a large polyp in the distal ileum with ileocecal intussusception. Evidence of previous bowel resection was present in the terminal ileum. Thorough investigation of the remaining gastrointestinal tract revealed two additional polyps in the proximal jejunum. The intussusception was reduced and a segment of ileum containing the polyp excised. The remaining polyps were individually removed through separate enterotomy incisions. Gross pathology of the excised polyps revealed the largest to measure 6 x 4 x 3 cm. Its microscopic appearance was that of a benign adenomatous lesion. The remaining polyps were slightly smaller with a similar microscopic picture.

Postoperative convalescence was complicated by a subcutaneous wound abscess which responded to antibiotics and drainage. Renal function gradually returned to normal, and the patient was dismissed on the twelfth postoperative day. She has since been asymptomatic.

Case Two

On September 2, 1957, a 16-year-old unmarried Negro girl was seen in the emergency ward of the University of Kansas Medical Center with the chief com-

From the Department of Surgery, the University of Kansas Medical Center, Kansas City, Kansas. Dr. Reed is an American Cancer Society Clinical Fellow.

plaint of abdominal pain of gradually increasing severity for 24 hours. The pain was described as cramping and was periumbilical. Nausea and vomiting had occurred two hours before admission. The patient stated that she had had a normal bowel movement 24 hours previously.

The patient had been operated upon four years previously at another hospital for "bowel trouble," but the exact nature of her illness could not be established. Her mother *(Case 1)* had been operated upon for ileocecal intussusception five weeks before admission of the daughter.

The patient was an acutely ill Negro girl. The rectal temperature was 101.2 degrees; blood pressure, 120 systolic and 70 diastolic; and the pulse rate was 140 per minute. Examination of the head and neck revealed pale conjunctivae. Numerous dark brown to black flat pigment spots measuring 0.1-0.3 cm. in diameter were noted on the buccal mucosa and lips. Similar areas were present on the palmar aspect of the hands. The abdomen was slightly distended. Bowel sounds were diminished, and tenderness with rebound phenomenon was noted in the lower abdomen. The remainder of the physical examination was non-contributory.

The hemoglobin was 6.2 grams per cent; hematocrit, 19 per cent, and the white cell count was 15,000 with 83 per cent polymorphonuclears. A urinalysis showed a mild pyuria (12-15 pus cells per high power field), one plus albuminuria and one plus glycosuria.

Exploration of the abdomen was performed on the evening of admission. An ilecocecal intussusception was found which could not be reduced and necessitated a right colectomy. A small easily reduced intussusception was also present in the proximal jejunum and two polyps were removed from this area through an enterotomy. The postoperative recovery was uneventful.

The specimen showed a polyp presenting at the leading edge of the ileocecal intussusception. None of the polyps showed microscopic or gross evidence of malignancy.

The patient was seen again in January, 1958, when she reported an episode of hematemesis and melena. Sigmoidoscopy confirmed the presence of blood. No source was found in the rectum. A barium enema was suggestive of polyps in the ileum. An upper gastrointestinal series was interpreted as normal. She has not returned for further examination.

Figure 1. Typical pigmented areas on the lower lip. Similar areas were noted on the buccal mucosa (Case 3).

Case Three

A 15-year-old Negro boy, the son of the patient reported as Case 1, was admitted to the Medical Center on November 11, 1958, with a complaint of cramping abdominal pain for seven hours. Vomiting had occurred three times. One month before admission he had had a similar attack which subsided spontaneously, and he had had numerous other less severe episodes during the past two years.

The physical examination was non-contributory except for numerous dark brown, smooth, pigmented areas 0.1 to 0.3 cm. in diameter on the lips and buccal mucosa *(Figure 1)* and a slightly distended abdomen which was moderately tender in the right lower quadrant.

The urinalysis and the white blood count were normal. The hemoglobin was 12.0 gram per cent, and the hematocrit was 41 per cent. A sickle cell preparation was negative. An x-ray of the abdomen showed multiple loops of distended small intestine.

A laparotomy was carried out eight hours after admission. Numerous polyps were found throughout the small intestine with an area of intussusception in the midportion of the jejunum. The leading point of the intussusception was a polyp. Four palpable polyps were removed from the small intestine by multiple enterotomies and the intussusception was reduced. The postoperative course was uneventful.

Microscopic examination of the polyps showed no evidence of malignant changes.

Discussion

Bartholomew *et al,* reported a familial incidence of approximately 40 per cent. An additional five per cent had peculiar pigmented areas without demonstrable polyps. This is a slightly higher incidence than reported by Staley.[32]

Jeghers *et al,* writes that although the genetic pattern is similar to colonic polyposis, this is a different entity. Males and females carry the factor. They believe a patient with spots also has polyps, usually throughout the gastrointestinal tract. A single pleiotropic gene is responsible for both characteristics, polyps and spots, but may be demonstrated to have one or the other. In the family from which the above cases have been reported, two additional children have the pigmented areas. One has abdominal colic intermittently; the other is asymptomatic. Five additional children do not have spots and are asymptomatic. The appearance of three well-documented cases in one family as well as the presence of pigment spots and symptoms in other members of the same family would lend support to the previously reported strong familial tendency.[8, 9, 11, 17, 20, 21, 26, 29, 34, 35]

The presence of pigment spots without demonstrable polyps has been reported.[3, 32] It is difficult to ascertain the number of individuals with only pigment spots because clinical or x-ray evidence of polyps may not appear for many years.

The pigmented areas are most commonly located on the lips and buccal mucosa,[3] and less frequently on the hands, feet and face. Although some are present at birth, most are reported as appearing in early childhood. They are usually one to five mm. in diameter, dark brown to black, with a smooth, hairless surface. Dark complexioned individuals are commonly affected although cases in blond individuals have been noted.[21, 23, 24, 33]

Miscroscopic examination shows melanin pigment arranged in vertical bands.[20]

The incidence of Peutz-Jeghers syndrome is difficult to determine. A review of the literature reveals approximately 90 well-documented cases including the cases reported here. That is not an accurate figure, however, because many cases are currently not confirmed by operation or clinical symptoms. With increasing awareness of the syndrome, one would anticipate a rapid rise in the reported incidence.

It has been noted that these polyps are present throughout the gastrointestinal tract, but are particularly prone to appear in the small bowel. As a matter of fact, some doubt as to accuracy of the diagnosis should be cast on cases in which polyps are absent in the small bowel. Bartholomew reports demonstrable polyps in the small intestine of sixty-seven patients with this syndrome. Polyps appear less frequently in the colon, rectum, stomach, and duodenum respectively. More than one polyp has been found in 80 per cent of the cases.

Signs and Symptoms

The appearance of colicky abdominal pain is the single most common complaint. The pain may be acute in onset with clinical signs of partial or complete bowel obstruction. The patient may experience recurrent attacks over several years which do not require surgical relief.[22] The onset of complete obstruction is usually due to intussusception,[10] and may necessitate operative intervention. Intussusception is a common occurrence in any small bowel tumor as reported by Camp. Anemia is a frequently associated finding, and may be of moderately severe degree.[4] Intermittent intestinal bleeding coincident with abdominal pain explains the anemia in many instances. The presence of typical pigment spots is the single most easily established feature of the disease.

Age of Onset

The onset of symptoms occurs most commonly during the third decade of life. However, cases have

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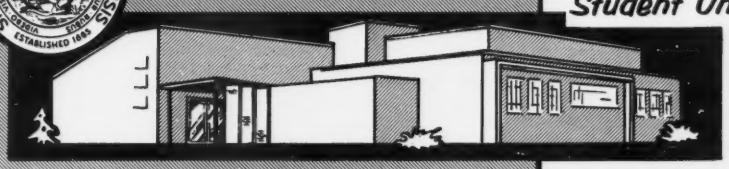

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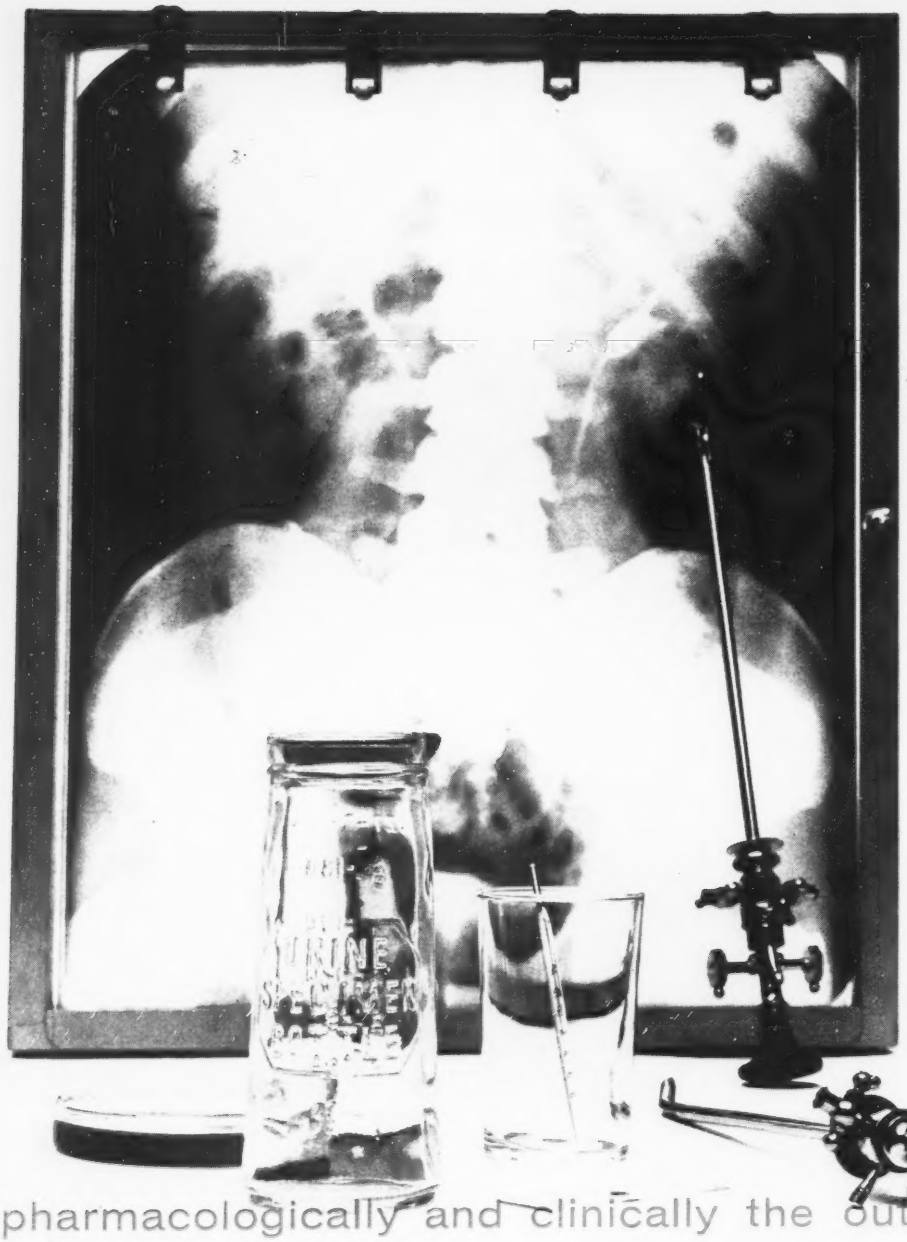

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been reported in children as well as in the elderly. Troxell described the disease in a 77-year-old man.[33]

Sex

There appears to be no predilection for the disease to appear predominantly in one sex.

Pathology of Polyps

Considerable controversy exists as to whether or not the polyps undergo malignant change or are benign or malignant at their outset. Jeghers reported malignant change in one case, as did Foster and others.[1, 4, 5] Although some authors report malignant change as being present, there has been no report of lymph node or distant metastasis.[36] It has also been suggested that these lesions are hamartomas.[3] The usual appearance is that of a benign adenomatous polyp.

Treatment

In view of the long natural history for the disease, it is desirable to use an approach to the acute episode which will conserve as much tissue as possible. Reduction of the intussusception and simple polypectomy by enterotomy will satisfy this goal when possible. A thorough exploration of the bowel should be carried out with particular attention to the small intestine. Many unsuspected polyps may be found and removed, thereby preventing postoperative or early return of obstructive symptoms. A more radical approach toward the local lesion may eventually deprive the patient of a major portion of the small bowel in view of the multiple operations that are required in some individuals.

Elective laparotomy searching for small intestinal polyps in patients with characteristic pigment spots or laparotomy in asymptomatic patients with radiologically noted polyps is not indicated. Operative intervention should be reserved for the patient with acute obstructive symptoms or for those in whom the diagnosis is in doubt.

In spite of the tendency to recurrent episodes of obstruction, the general outlook is good. The absence of reported cases of death as a result of metastatic disease is encouraging. Most patients remain essentially asymptomatic between episodes.

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Hypnotic Wart Treatment

(Continued from page 151)

natural healing powers of your skin. It is going to help your skin to get rid of these warts. It will help your skin to exercise its natural healing power that much faster." Following this, the patient was permitted to remain in hypnosis for a few minutes and then brought out. There were three hypnotic sessions in all; the first lasted a half hour, the others requiring only twenty minutes each. The sessions were spaced at weekly intervals. At the end of the first week the patient claimed to note a definite decrease in the size of the warts. Following the third session the warts had undoubtedly disappeared and at this writing (two months later) have not reappeared. The treatment, then, appears to be quite simple; the time in this case required two weeks less than the minimum time reported by Sinclair-Gieben and Chalmers.

In view of the fact that spontaneous recovery from warts is not uncommon the question might conceivably be raised: How do we know it was the hypnotic treatment that was responsible for the cure, and not, indeed, such spontaneous recovery? Conceivably, one might wish, in answering this question, to invoke the logic of the immediate and particular situation. That is, it might be argued that, far from revealing tendencies to spontaneous recovery the patient actually reproduced new warts immediately on surgical excision. Consequently (it might be contended) this tendency to reproduce the warts was effectually neutralized by the hypnotic treatment. However, instead of invoking this kind of argument, I should prefer to remain within the general logic of clinical medicine. That is, the physician must face the fact that in *any* given clinical treatment of a patient, no matter what the procedure, it is quite simply not possible to claim within the logic of empiricism that it is the *treatment* which produces the effect on the patient.

Placebo Effect

If a physician uses medication on a patient who has complained to him, "Dr., I can't sleep!" and the patient subsequently reports improvement in sleep, the physician is not warranted in claiming knowledge that this sleep was induced by the chemical characteristics of the drug. There *may* have been "spontaneous recovery" or there *may* have been a "placebo effect" such that *anything* given the patient by the physician (so long as it was not harmful) might have resulted in inducing sleep. Consequently, the physician is justified in claiming knowledge that *the particular drug administered* was the sleep-inducing agent if, and only if, he can point to or invoke adequate experimental evidence to this effect. In other words, if someone has done an experiment with this drug, controlling adequately for all of these other variables, which experiment justifies the conclusion that *this drug* is the sleep-inducing agent, then (and only then) the physician is justified in claiming that *the drug administered to the patient* was probably the sleep-inducing agent.

Following this logic of clinical medicine it must be said that in the present case the efficacy of the hypnosis as the agent responsible for the disappearance of the warts can be claimed only in conjunction with experimental evidence controlling for spontaneous remission. The experiment reported by Sinclair-Gieben and Chalmers provides just such evidence. These investigators controlled for this variable with admirable rigor, using patients with bilateral warts and treating only one side. In their main experiment, immediate improvement was reported and observed only on the treated side in ten patients out of ten who met the criterion of ability to carry out a post-hypnotic suggestion. (One patient failed to improve, but this patient did not meet the criterion.) The statistical probability corresponding to these results (i.e., ten improvements out of ten) is well beyond the .01 level of confidence.

Department of Psychiatry
University of Kansas Medical Center
39th and Rainbow
Kansas City 12, Kansas

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A person remains immature, whatever his age, as long as he thinks of himself as an exception to the human race.—*Harry A. Overstreet*

Inhibitors of Tumor Growth

N-Chloroacetyl β Alanine, N-Chloroacetyl Glutamic Acid, and Azaserine

ROBERT W. BROWN, M.D.; *and* SANTIAGO GRISOLIA, M.D.,
Kansas City

Nineteen patients with histologically proven malignancies were treated with these agents and their findings are reported in this article.

IT HAS BEEN SHOWN previously that the N-chloroacetyl derivatives of β alanine and glutamic acid potentiate themselves as inhibitors of tumor growth in rats.[1]

The possibility of further potentiating the action of these inhibitors with azaserine® (O-diazoacetyl-L-serine) was investigated and found promising. Intraperitoneal administration of ten micromoles each of chloroacetyl β alanine and of chloroacetyl glutamic acid or of 33 gammas of azaserine had little, if any, effect on the growth of Ehrlich ascites cells with 20 gram mice. However, when combined they delay growth up to 18 days *(Figure 1)*. Ceasing administration resulted in renewal of growth at pretreatment rate *(Figure 2)*.

Dr. Brown is from the McIlvain Laboratories, University of Kansas Medical Center, Kansas City, Kansas; and Veterans Administration Hospital, Kansas City, Missouri and Dr. Grisolia is from the McIlvain Laboratories, University of Kansas Medical Center.

Toxicity Inversely Proportional to Amount of Tissue

It is noteworthy that the weak toxicity of the chloroacetyl compounds was inversely proportional

TABLE I

DIAGNOSIS, DURATION, AND PREVIOUS THERAPY IN PATIENTS TREATED WITH CHLOROACETYL β ALANINE, CHLORACETYL GLUTAMIC ACID AND AZASERINE*

Patient Number	*Primary Carcinoma*	*Duration Before Treatment*	*Previous Treatment*
1	Skin, squamous cell	13 months	X-ray, 5,000 r.
2	Breast	5 years	None
3	Breast	30 months	X-ray
4	Metastatic adenocarcinoma to liver	5 months	Nitrogen mustard
5	Uterus	34 months	Panhysterectomy
6	Kidney	15 months	Nephrectomy, x-ray, nitrogen mustard
7	Lung, squamous cell	6 months	Nitrogen mustard, x-ray
8	Lung, squamous cell	10 months	None
9	Pancreas	12 months	None
10	Lung, adenocarcinoma	4 months	None
11	Lung, anaplastic	5 months	None
12	Lung, anaplastic	12 months	None
13	Stomach	8 months	Nitrogen mustard
14	Breast	10 months	Radical mastectomy, x-ray
15	Lung, anaplastic	1 month	None
16	Lung, adenocarcinoma	3 months	Laparotomy, with adrenalectomy
17	Lung, anaplastic	10 months	Nitrogen mustard, x-ray
18	Colon,** adenocarcinoma	16 months	Partial colectomy
19	Kidney**	2 months	None

* Objective findings of tumor regression were observed in none of the patients.
** Patients 18 and 19 tolerated prolonged therapy without side effects.

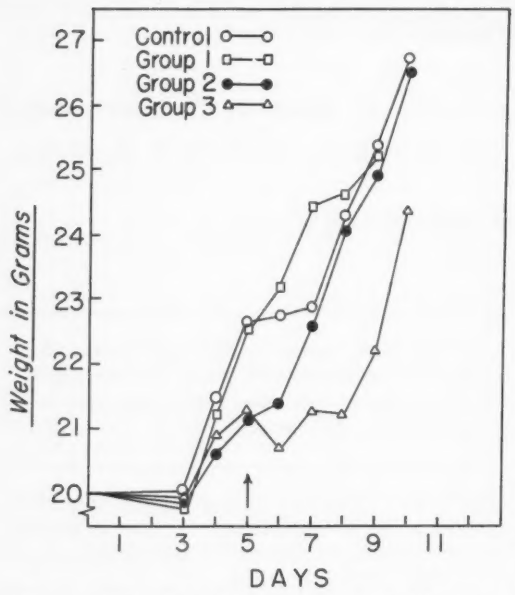

Figure 1. The effect of intraperitoneal administration of chloroacetyl amino acids and of azaserine on growth of Ehrlich ascites cells.

Each group (six animals, expressed in the graph as the average weights per group), was inoculated with about one million Ehrlich ascites cells. As indicated by the arrows on the fifth day each group was injected intraperitoneally as follows: 0-0, 0.5 ml. saline; □-□, 0.5 ml. of neutralized solution of 10 micromoles each chloroacetyl β alanine and chloroacetyl glutamate; •-•, 0.5 ml. of saline solution containing 3? micrograms of azaserine; Δ-Δ, 0.5 ml. each of the chloroacetyl amino acids and of azaserine solutions. Injections were repeated on the sixth and seventh days.

to the amount of tumor tissue. These findings indicated the desirability of testing combinations of inhibitors which may be acting at several bio-chemical levels, for arresting and perhaps eradiction of neoplastic growth. After toxicity studies the compounds were tested in increasing single doses in humans with far-advanced carcinoma, until maximum calculated dose (100 micromoles for each amino-acid derivative as the sodium salt and from one to 1.25 mg. azaserine per Kg.) was reached.

Nineteen patients with histologically proven malignancies were treated. Seventeen patients received a series of three intravenous infusions on successive days. Two patients *(No. 18 and 19)* received, in addition, a weekly infusion for three months. No change in tumor size was observed. Four patients had favorable clinical response with decreased fever and pain but not directly attributable to the medications. Toxic manifestations were mild, nausea, and vomiting in nine patients and transient mental confusion in two patients. Table I shows the tumor origin, duration of symptoms prior to treatment, and previous therapy.

As seen in the clinical trials the combinations were not effective in altering the course of the disease or size of tumor mass. Moreover, the doses used resulted in no depression of bone marrow elements.

Potentiating Effect

On the other hand, the experimental evidence that inhibitors such as the ones used here have a potentiating effect in retarding tumor growth and are without significant toxic side effects in humans indicates the desirability of testing combinations of inhibitors acting at several bio-chemical levels.

We wish to extend our thanks to Dr. M. Chiga for help with some of the studies, to an institutional grant of the American Cancer Society, to a grant of the Kansas Cancer Society, and to Dr. C. J. Gajewski of Parke Davis Company for the azaserine.

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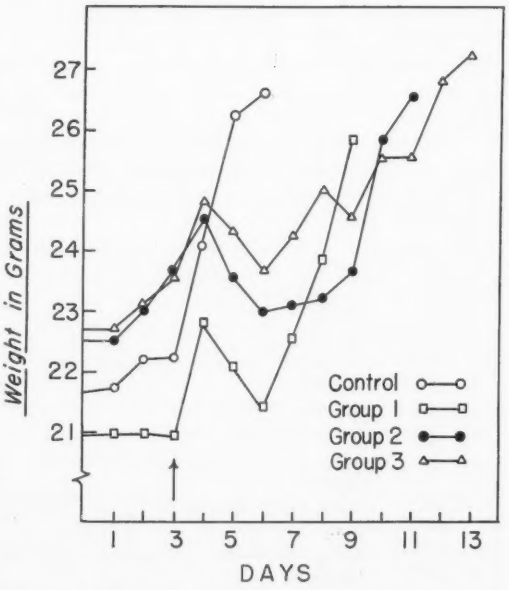

Figure 2. The effect of length of administration of chloroacetyl amino acids and azaserine on growth of Ehrlich ascites cells.

The experimental conditions were as for *Figure 1*, except that group one was treated for three days, group two for five days and group three for seven days. In all experiments injections started the third day following inoculation of Ehrlich ascites cells, as indicated by the arrow.

Tranquilizers? Ataractics? Sedatives?

The So-Called Tranquilizers Are Reviewed and Classified

JESSE D. RISING, M.D.,* ***and*** **EDWARD J. WALASZEK, Ph.D.,**** ***Kansas City***

EVOLUTIONISTS HAVE PONDERED the question, "What is man?" without notable success for a good many years. Such terms as "tool-maker," "fire-maker," and "user-of-language" have been applied, each with the assumption that the acquisition of the indicated skill marked the separation of the human species from the bestial multitude; but all have been placed in doubt by archeological findings except for speech which, although it may be the best of the criteria, cannot be traced by archeological methods. Another characteristic might well be investigated, for there is much evidence to favor the appellative "man-the-worrier." So far as we know the earliest and most primitive of the humankind have resorted to naturally occurring substances—we would call them phrenotropic drugs today—to allay their anxieties and ennui and to give them peace of mind and courage.

No one has estimated the antiquity of alcohol, hashish, pyote, tobacco, coffee, tea, and coca to name a few of the "delight makers," but they are of unfathomed antiquity; and, for whatever it may signify, the stimulants have perhaps enjoyed greater use than the depressants. It is indeed true that pharmacology is older than agriculture.

Whether, as some contend, there has been an increasing use of stupifying drugs since the introduction of the barbiturates in the early years of this century is really somewhat doubtful, but there can be no question about the magnitude, probably excessive, of this phase of the drug industry, and the interest of the medical profession and the laity alike rose to an unprecedented pitch with the introduction of the tranquilizers (called by some ataractics) some five years ago.

Because they were called by a new and, in therapeutic circles, previously unused name it has been widely assumed that these drugs share some major characteristics and differ fundamentally from previous sedatives and hypnotics. A search of the dictionaries does not, however, confirm this assumption. Indeed, it appears that the word "tranquilizer" is synonymous with "ataractic," and it is difficult to distinguish from "sedative" which is defined as an adjective which means "tending to calm, moderate or tranquilize."

* Associate professor, medicine and pharmacology, University of Kansas School of Medicine, Kansas City, Kansas.
** Associate professor of pharmacology, University of Kansas School of Medicine, Kansas City, Kansas.

The enormous commercial success of the word "tranquilizer" has led drug manufacturers to search for other semantic gold mines, and they have coined such beguiling terms as "calmative," "psychosedative," and "neurosedative" to mention a few.

Tranquilizer Pharmacology

What is the real substance that supports these terms? In attempting to answer this question we shall first gather the tranquilizers together into their main groups and then examine their pharmacological characteristics so that we can find the actions which are common to the whole as well as those which are unique. The tranquilizers in common use are easily divided into four main groups which have been subjected to rather extensive pharmacological scrutiny with the aim of delineating their mechanisms and loci of action. These are (1) the phenothiazines, (2) the Rauwolfia alkaloids, (3) diphenylmethane derivatives, and (4) substituted propanediols (and butanediols).

In the so-called tranquilizers the medical profession has been given a group of drugs that have therapeutic possibilities beyond those of previous agents. It is probably not wise to classify them indiscriminately as tranquilizers, but rather to recognize each of the major groups for its unique pharmacologic, therapeutic, and toxic possibilities.

The type drug of the phenothiazines is chlorpromazine. Members of this group have adrenolytic, anticholinergic, and antihistaminic characteristics, but the several drugs are endowed with them in different proportions, and some members of the group have been used almost exclusively as antihistaminic drugs *(Table I)*.

The Rauwolfia alkaloids, typified by reserpine, have the ability to release the biogenic amines (epinephrine, norepinephrine and serotonin) from sundry tissues. Whether or not as a result of this action, drugs of this group apparently cause central depression of the sympathetics with the result that there

TABLE I

TRANQUILIZERS
PHARMACOLOGIC EFFECTS

	Rauwolfia	*Phenothiazine*	*Diphenylmethanes*	*Meprobamate*
Anticholinergic		+	++	
Adrenolytic		+++		
Antihistaminic		++	++++	
Release biogenic amines	++++			
Potentiate barbiturates	++	+++		
Antagonize strychnine	0	0	0	++++

is a parasympathetic predominance, and they superficially seem to act as cholinergic agents in many respects.

The diphenylmethane drugs have actually been longest used as antihistaminics, but they also have anticholinergic or atropine-like effects. Hydroxyzine is an example of this group, most members of which were originally produced in an effort to secure marketable anthihistaminics only to be shelved when it was discovered that their tendency to cause excessive sedation made them unsuitable for this purpose.

The propanediol group, represented by meprobamate, act as central muscle relaxants which have the ability to abolish strychnine convulsions but not those induced by pentylenetetrazol which indicates a locus of action in the internuncial neurone. Their psychic effects were discovered later.

This is a motley group of drugs to place in the same category. They must have something in common —if not a common mechanism at least a common site of action should be discernible. How *do* they work?

Mechanisms of Action

Fundamentally, sedation and tranquilization can result from excitation of inhibitory centers of the brain as well as from inhibition of the excitatory centers. Furthermore, it must be remembered that stimulants can cause tranquility through the relief of tension that goes with an elevation in mood such as can be observed with the judicious use of cocaine or amphetamine.

In order to pinpoint the actions of pharmacologic agents of this type and define their mechanisms it is important to have a good working knowledge of brain physiology, including brain biochemistry. This is where we run into difficulties! But there are certain clues which allow us to formulate hypotheses which can be put to test with the expectation of increasing our knowledge of this field bit by bit. It has long been known that acetylcholine is a neurohumor of importance in ganglionic transmission, and there is evidence that it functions to facilitate interneuronal transmission in the brain. Some authorities are of the opinion that the biogenic amines such as epinephrine, norepinephrine, and serotonin are neurohumors which impede interneuronal transmission in the brain. Even the ubiquitous histamine is thought by some to be an important neurohumor. There is even some indication that emotional states occur in concert with fairly typical neurohumoral changes; that anxiety, fear and depression can be equated with the flight component of the fight-or-flight response and are characterized by a preponderance of epinephrine effect, whereas in anger and aggression (fight component) there is an excess of norepinephrine. Another neurohumoral agent is a polypeptide called Substance P. This substance seems to be a sedative and to inhibit polysynaptic neuronal pathways. Since it is naturally present in the brain some investigators suggest that the role of Substance P is that of a physiological tranquilizer.

These speculations become more intriguing when we consider the fact that so many of the tranquilizers have effects that are related to the substances just mentioned. The phenothiazines, as previously noted, have antiserotonin, anti-epinephrine, anti-acetylcholine, and antihistamine effects. Rauwolfia alkaloids release serotonin, epinephrine and norepinephrine. Finally, the diphenylmethanes are both antihistaminic and anticholinergic. Meprobamate and other members of the propanediol group, which act as central muscle relaxants, act synergistically with Substance P.

Anatomic Sites of Action

Up to this point tranquilizers appear not to be unique or to have any significant property in common. Perhaps an examination of the anatomic sites of action will be more revealing. The phenothiazines are known to depress the brain stem alerting system

TABLE II

TRANQUILIZERS
SITES OF ACTION

	Rauwolfia	*Phenothiazine*	*Diphenylmethanes*	*Meprobamate*
Depress MDAS . Stim.		++++	++++	
Depress thalamus				+++
Depress hypothalamus	+++	+++		++
Stimulate amygdala	+++	++++		

which is important in maintaining the brain in the waking state, and which has widely been assumed to have some importance in the control of the emotions *(Table II)*. They also depress the hypothalamus which is undoubtedly an important center for the integration of emotional responses. Finally, they disrupt the rhinencephalon or limbic system which is a phylogenitically ancient and important integrative center and is thought to be of fundamental importance in man as a center for coordinating the baser or animalian components of his psyche. This disruption is not accomplished by depression, but seems rather to be the result of over-stimulation of the amygdaloid nucleus, an important way station in that part of the limbic system which is sometimes called Papez circle.

The diphenylmethanes also depress the brain stem alerting system, but other sites of action in the brain are not understood. It is hazardous to ascribe much importance to depression of the MDAS because atropine, among others, very effectively depresses this structure without having sedative or tranquilizing effects.

The Rauwolfia alkaloids on the other hand stimulate the brain stem alerting system (mesodiencephalic activating system or MDAS), but this is offset by a depression of the hypothalamus. The limbic system is, again, disrupted by overstimulation of the amygdala.

Less is known about meprobamate, but it seems that it depresses the thalamus and limbic system.

Behavioral Effects

So far we have not been successful in separating the new drugs, the tranquilizers, from other medications or in pulling them together into a neat package. Perhaps their behavioral effects *(Table III)* will throw more light on the subject. Meprobamate, Rauwolfia and the phenothiazines have a taming effect on monkeys; in other words, appropriate doses of these drugs can render these aggressive animals quite docile without putting them to sleep. This particular effect is of limited importance in human medicine, if one excepts the simian reactions of certain psychotics, and it is not often recognized that, milligram for milligram, the phenothiazines are about as potent hypnotics as secobarbital.

Much has been made of the ability of the tranquilizers to antagonize conditioned responses. Meprobamate apparently lacks this characteristic, but it is prominent in the phenothiazines and Rauwolfia alkaloids. The fly in the ointment here is that morphine, alcohol and atropine—a disparate group—share this feature with the two favorite tranquilizers. On the other hand, it has been found that meprobamate reduces the fear behavior in water fowl during the optimum period for imprinting, but makes it almost impossible to imprint the birds. After the meprobamate has worn off imprinting can be accomplished at a time when the critical period for imprinting would normally be passed. Pentobarbital interferes with imprinting but does not extend the critical period, whereas chlorpromazine does not interfere with imprinting but *does* prolong the critical period. These are intriguing observations, and doubtless have fundamental importance which will be elucidated as more work is done. At the moment, however, it is a bit hazardous to project these concepts too far into human therapeutics.

TABLE III

TRANQUILIZERS
BEHAVIORAL EFFECTS

	Rauwolfia	*Phenothiazine*	*Diphenylmethanes*	*Meprobamate*
Depress conditioned response	+++	+++		
Prevent imprinting ...		0		+++
Prolong imprint period .		+++		+++
Taming effect on monkeys	++++	++++		++++

A Semantic Trap

For the moment, then, it appears that our quest has only demonstrated that no pharmacological action is unique to the tranquilizers, and none is common to them. If we are to deal with these drugs rationally it is important not to fall into a semantic trap and lump them together in one group under the name "tranquilizers." We should, on the other hand, define their actions and mechanisms and classify them on that basis. It seems certain that, at least at the level of the practicing physician—the therapeutic level—the introduction of the terms "tranquilizer" and "ataractic" have led to the uncritical use of drugs and has done more harm than good. Something can be said for completely abandoning the term "tranquilizer" rather than continuing to use it and be led into sloppy thinking and haphazard therapeutics.

Until recently the only alternate or complement to psychotherapy in the treatment in acute and chronic anxiety states, obsessive-compulsive neuroses, psychotic agitation and mania, toxic delirium (as in alcoholism), and the symptoms accompanying drug-withdrawal was drug therapy with "standard" sedatives and hypnotics. The bromides are in many ways ideal sedatives, but they are too mild in action to be especially useful in the treatment of severe agitation, and they tend to produce unpleasant side effects

TABLE IV

TRANQUILIZERS
AUTONOMIC SIDE-EFFECTS

	Rauwolfia	*Phenothiazine*	*Diphenylmethanes*	*Meprobamate*
Indigestion	+++			
Peptic ulcer	+++			
Diarrhea	+++			
Fecal impaction		+		
Impotence	++	++		
Hypotension	++	+++		

such as skin rashes on prolonged use. The worst complication associated with their prolonged use is, of course, the well known bromide psychosis. The other drugs mentioned are, in essence, hypnotics rather than sedatives, and they tend to produce excessive drowsiness when used in the treatment of the conditions mentioned. The newer drugs, which are the subject of the present discussion, were introduced in the hope that they would produce a calming or taming effect in patients without making them too sleepy to carry on their routine activities.

Their Chief Benefits

Among the chief benefits of the tranquilizers has been the stimulus which they have given to research in psychophysiology and psychopharmacology, and these fields are now receiving long overdue attention. It may be stated, in addition, that most of these agents are effective *aids* to psychotherapy. It must be emphasized that psychotherapy is the treatment of choice, and that the tranquilizers give the patients needed support during the earlier phases of psychiatric treatment. In addition, they decrease excitement and over-activity as well as agitation and furor, and they minimize the patient's *reactions* to delusions and hallucinations without having any definite effect on disordered ideation. These actions combine to make patients more accessible for psychotherapy.

There is no such thing as a drug that has no deleterious side effects or toxic actions, and physicians must remember that the tranquilizers are potent agents which have numerous toxic potentialities. It is important, therefore, to recognize that, while they have an important place in modern therapeutics, their use is attended by numerous hazards; and physicians must know enough of their indications and pharmacology to use them wisely. We certainly are not justified in employing them in the treatment of every person who is a little nervous or who poses a problem in psychotherapeutic management for the family physician. Many jokes have arisen surrounding the theme of tranquilizers, and even some serious literature has appeared concerning the possibility of achieving nirvana. Perhaps this is as good a place as any to point out that, if we can believe the lessons of history, a little anxiety is a very good thing.

Side-Effects

The effects of drugs are mediated through the various physiological mechanisms of the body; and there are effects, therefore, upon many aspects of bodily function as well as upon mood and other general aspects of psychological functioning. Medicine has long been aware not only of the physiological but also of the psychological side effects of many of its therapeutic agents. The physician has always had to calculate the therapeutic value of each drug for a specified purpose for the patient in question as balanced out by possible or probable undesirable side effects of either a physiological or psychological nature. The ability to make such decisions properly represents a large part of the successful practice of medicine. In the case of the new psychologically significant drugs the focus of the physician is primarily upon the psychological effects, while at the same time being alert for the physiological ones. It is well to remember that with these drugs the possible side effects are of both a psychological and a physiological nature.

Rauwolfia Derivatives

Rauwolfia derivatives were the first tranquilizers to be designated as such, and they enjoyed some reputation as calming agents for various states of hyperactivity. They were largely replaced by the phenothiazine, chlorpromazine, which has since been partially replaced by the newer phenothiazine derivatives.

The chief adverse behavioral effect which has been attributed to the Rauwolfia derivatives is psychotic depression, and many patients have actually committed suicide while under the effect of the drugs.

TABLE V

TRANQUILIZERS
CNS TOXICITY

	Rauwolfia	*Phenothiazine*	*Diphenylmethanes*	*Meprobamate*
Parkinsonism	++	+++		
Grand mal seizures	++	+++		
Withdrawal seizures				++
Overdose convulsions			++++	

They also tend to cause undue lethargy and social withdrawal, and many patients complain of bizarre dreams. They share with the phenothiazine group the ability to cause parkinsonism and epilepsy, and their effects on the autonomic nervous system lead to such gastrointestinal symptoms as nausea, hyperchlorhydria —and even activation of peptic ulcer, flatulence and diarrhea. Nasal congestion is often complained of. Impotence is occasionally a disturbing side effect. Some patients retain sodium and water while on Rauwolfia medication, even to the point of clinical edema; and a few cardiac patients have developed frank heart failure while on this type of medicine, their decompensation subsiding promptly on discontinuing the medication. A point to remember about the Rauwolfia derivatives is their onset of action and duration of action. With the reserpine group cumulative effects are seen, and this requires a careful adjustment of dose. Furthermore, the onset of the tranquilizing action is such that the tranquilizing effect is seen only after a few days, and this effect persists after the withdrawal of the drug. If therapy with another shorter acting tranquilizer is contemplated it would be important not to begin treatment too soon after the withdrawal of the reserpine or an alarming synergistic effect might be noted.

The Phenothiazines

The clinical effects of phenothiazine tranquilizers are numerous and varied. They are especially effective in the control of excessive agitation and hyperactivity in both psychotic and psychoneurotic patients, and have been quite useful in controlling alcoholic delirium as well as drug-withdrawal syndromes. They early found a use as effective antemetics, and hiccups may respond to treatment by members of this group when all other types of therapy have failed. They have also been employed with possibly less effect in the treatment of pruritis.

Phenothiazines can, on the other hand, cause such adverse behavioral effects as restlessness, nightmares, social withdrawal, depression, unreality feelings, and even hallucinations and illusions. They are known to cause such central nervous effects as epileptiform seizures at times, even in persons who have had no clinical or EEG tendency toward them, and extrapyramidal syndromes which may mimic parkinsonism exactly or be exceedingly bizarre. Their effects on the autonomic nervous system may lead to very marked nasal congestion or constipation, the latter occasionally reaching such severity as to cause fecal impaction. Impotence is not an uncommon result of treatment. They may, of course, cause the whole gamut of allergic reactions, and have been known to cause dermal photosensitivity, dermatitis, purpura, and agranulocytosis. Whether the jaundice which some of them cause is allergic has been debated, but it is usually attributed to this mechanism. These agents are also effective synergizers of analgesic, sedatives and anesthetics and they can be effectively used to reduce the dosage of other drugs. In this regard it is important to remember this facet of their action in order to avoid inadvertent and unwanted potentiation of other central nervous system depressants.

TABLE VI

TRANQUILIZERS
ADVERSE BEHAVIORAL EFFECTS

	Rauwolfia	*Phenothiazine*	*Diphenylmethanes*	*Meprobamate*
Somnolence and lethargy	+++	+++	+++	+
Restlessness and nightmares	+++	++		
Social withdrawal	++++	++		
Psychotic depression	++++	++		

TABLE VII

TRANQUILIZERS
ALLERGIC REACTIONS

	Rauwolfia	*Phenothiazine*	*Diphenylmethanes*	*Meprobamate*
Jaundice		+		
Agranulocytosis		+		
Purpura		+		
Dermatitis		+		+

Propanediol Group

Only one representative of the propanediol group has been widely used, and this is meprobamate. It has enjoyed some popularity in the treatment of muscle tension headache and sundry other painful conditions which have been assumed to be a combination of "nervousness" and muscle spasm. It has not been notably effective in this regard, but has achieved wide popularity as a simple sedative and hypnotic. Patients appear to respond to meprobamate rather irregularly: some feeling little or no effect at standard doses (400 mg. two to four times daily) while others have a hypnotic effect from a single dose of 200 mg.

The side effects of meprobamate are rather like those of the barbiturates, and patients who have taken high doses of the drug for long periods may have a withdrawal syndrome characterized by epileptiform convulsions. This drug is essentially ineffective in the

treatment of major psychiatric disorders. Adverse behavioral effects and toxic effects on the central nervous system are, in general, considerably less than with Rauwolfia and phenothiazine agents, and effects on the autonomic system are unimportant. Allergic reactions can, of course, occur, but they are by no means as frequent as with the phenothiazines.

The Antihistaminics

The diphenylmethane derivatives are essentially sedatives and hypnotics, and are quite properly classified as sedative antihistaminics. They are relatively safe sedatives, and, used as hypnotics, they are more effective in geriatric practice than the older hypnotics which have a strong tendency to cause excitement and delirium. These drugs are, of course, not entirely devoid of this potentiality, but it is much less pronounced in them than in most of the other agents which have been used. In high doses these drugs cause excitement, and toxic doses cause convulsions. Children are particularly prone to have severe convulsions—even resulting in death—from taking a large number of tablets or capsules of drugs in this group. Otherwise they are relatively non-toxic agents.

Summary

Effective use of these drugs in human therapeutics requires a basic knowledge of their pharmacology and an understanding of their indications and limitations, especially from the psychiatric point of view. They are not a substitute for the doctor-patient relationship, for the type of psychotherapy which every family physician practices (often unwittingly), or for major psychotherapy. Neither are they entirely benign because they can, even when used with great caution and for the best of indications, cause very severe, often frightening, and occasionally fatal reactions. Physicians who accept them as the panacea for all "nervousness" do both the drugs and their patients a grave injustice.

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(Continued from page 118)

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Primary Aldosteronism

Report of Two Cases and Review of the Literature

ROBERT T. MANNING, M.D.; MAHLON H. DELP, M.D.; C. FREDERICK KITTLE, M.D.; ROBERT W. WEBER, M.D.; *and* FRANK C. BROSIUS, M.D., *Kansas City*

Two cases of primary aldosteronism (Conn's syndrome) are reported. One patient received the spirolactone, SC-9420, with balance data indicating that the drug blocked the effect of aldosterone on the renal tubules. Both patients had excellent results following surgical removal of adrenal adenomas.

The literature is reviewed with respect to Conn's syndrome and 34 cases are tabulated. The most frequent presenting complaints were weakness and disturbed fluid balance. All had hypertension, low serum potassium, and diminished renal concentrating and acidifying capacity. Electrocardiograms almost always showed changes consistent with electrolyte abnormalities.

THE CLINICAL SYNDROME resulting from excessive production of aldosterone by the normal or abnormal adrenal has been well delineated. First described by Conn in 1955 at least 32 cases have been reported since his original report. This paper adds two more cases and demonstrates the results of use of the aldosterone antagonist, SC-9420,* in one case.

Case Reports

Case 1. A 43-year-old white woman was admitted for the first time on April 12, with a chief complaint of high blood pressure of 18 years duration. She had had morning headache and episodic weakness for two years. No history of cardiac, pulmonary, or renal disease was obtained except for one episode of painless hematuria the year before. Her appetite had been diminished for two years. She had had numbness and tingling of the hands several years before admission.

The patient was a well developed but thin woman without edema. The recumbent blood pressure was 210/120; standing, 220/115; and the pulse was 90. Examination of the skin showed some vasomotor instability. A grade I hypertensive retinopathy was present. The ears, mouth, and throat were negative. There was mild venous distention of the neck veins. The lungs were clear to auscultation and percussion. The heart was moderately enlarged to percussion, and there was a grade I basal, systolic murmur. Abdominal examination showed a right upper quadrant surgical scar. The liver was percussed five cm. below the right costal margin; the spleen was not palpable. The peripheral pulses were equal and 4+. The neurologic examination was within normal limits.

Laboratory: Urine specific gravity ranged from 1.004 to 1.015. All urine specimens were alkaline. There was a trace to two plus albuminuria and occasional white cells. The red cell count was 4.34 million; hemoglobin, 13.5 grams; white count 5,650 with 59 per cent polymorphonuclears, 29 per cent lymphocytes, one per cent basophils, ten per cent monocytes, and one per cent eosinophils. The VDRL was non-reactive. The serum calcium was 4.1 mEq/L; phosphorous, 1.8 mEq/L; NPN, 33 mg per cent; creatinine, 1.3 mg per cent; sugar 89 mg per cent; sodium, 144 mEq/L; potassium, 2.8 mEq/L; CO_2, 36.2 mEq/L; chloride, 103 mEq/L; and BUN, 10.5 mg per cent. Glucose tolerance revealed fasting sugar of 83 mg per cent; one hour 145, two hours 165, three hours 155, and four hours 117. Serum iron was 125 gamma per cent. The 24-hour urine contained 15 mEq. of sodium, 14 mEq. of chloride, and 10 mEq. of potassium. Urine concentration test showed maximum concentration of 1.008. The tuberculin test with PPD was negative; and the histoplasmin was positive. Urea clearance was 34 ml. per minute, maximum clearance. Urinary 17-hydroxy steroid excretion was 11.2 milligrams in 24 hours; 11-ketosteroids, 10.8 milligrams in 24 hours. Serum PBI was 6.3 gamma per cent; I^{131} uptake was 24 per cent in 24 hours. Catecholamine excretion was not increased. PSP excretion was 61.5 per cent with 20.5 per cent in 15 minutes. The LE preparation was negative. Total serum bilirubin was 0.7 mg per cent; direct, 0.1 mg per cent; alkaline phosphatase, 2.0 mM units; albumin, 4.8 gm per cent; gamma globulin, 1.5 gm

From the Department of Medicine and the Department of Surgery, University of Kansas Medical Center, Kansas City, Kansas.

* Kindly supplied by Dr. Clarence L. Gantt, G. D. Searle Co.

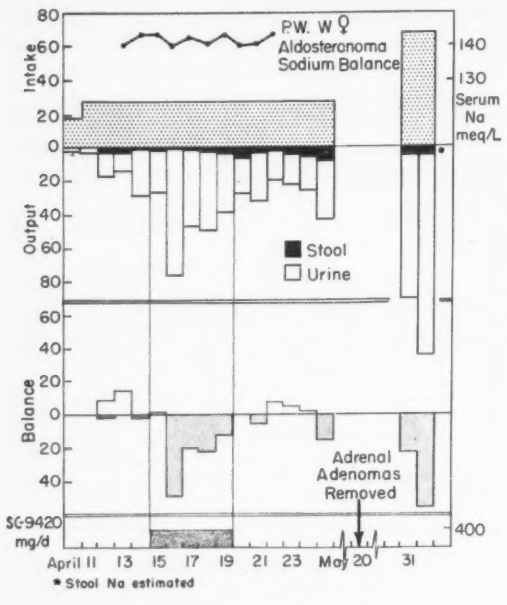

Figure 1

per cent; total cholesterol, 230 with 62 per cent esters. An electrocardiogram showed prolonged QT interval suggesting electrolyte disturbance. The chest x-ray showed cardiac enlargement with some evidence of pulmonary congestion; the fluoroscopic examination was otherwise within normal limits. An intravenous pyelogram showed normal kidney function and architecture.

Clinical Course

The patient remained relatively asymptomatic while in the hospital, and she was discharged on a 2,000 calorie, low fat, low cholesterol, 500 milligram sodium diet. In June she complained of a severe headache with nausea and vomiting, and at that time the serum sodium was 143 mEq/L; potassium, 5.0 mEq/L; chloride, 106 mEq/L. Her blood pressure was 210/120. In October she continued to complain of headaches, her weight was 125 lbs., and her blood pressure, 220/130. She was now taking potassium chloride regularly. Her serum sodium was 142 mEq/L; potassium, 3.5 mEq/L; chloride, 107 mEq/L. In May, the next year, she felt well, and was still taking potassium. She had had no muscle weakness or edema. Her blood pressure was 220/130; sodium, 140 mEq/L; potassium, 3.3 mEq/L; CO_2, 26.2 mEq/L; and chloride, 107 mEq/L. In November her sodium was 140 mEq/L; potassium, 3.7 mEq/L; CO_2, 33.0 mEq/L; and chloride, 101 mEq/L. She was referred to Dr. Jerome Conn in April, two years following first admission, and, after study at the University of Michigan Hospital, she was explored and the left adrenal with two small adenomas was removed. At that time her serum sodium was 143 mEq/L; potassium, 2.7 mEq/L; chloride, 103 mEq/L; CO_2, 30 mEq/L. She was seen in follow-up in October, at which time her blood pressure was 160/90; serum sodium was 137 mEq/L; potassium, 4.5 mEq/L; and she was asymptomatic.

Case 2. A 51-year-old housewife was admitted for the first time in April, 1958 with complaints of high blood pressure and visual loss of five years and eight months duration, respectively. The physical examination revealed her blood pressure to be 210/100, and she had a grade III hypertensive retinopathy and left cataract. Her serum sodium was 141 mEq/L; potassium, 2.8 mEq/L; chloride, 93 mEq/L; CO_2, 32 mEq/L. She was discharged on a 1400 calorie, 40 gram fat, 1650 mg. sodium diet.

No further visual impairment developed, and she admission in April, 1959, when she had a "blackout spell" followed by a severe, continuous, frontal headache. On admission she was acutely ill, her blood pressure was 220/110, her pulse was 78. There was a grade III arteriolar spasm with mild papilledema on the right. The left fundus could not be seen be-

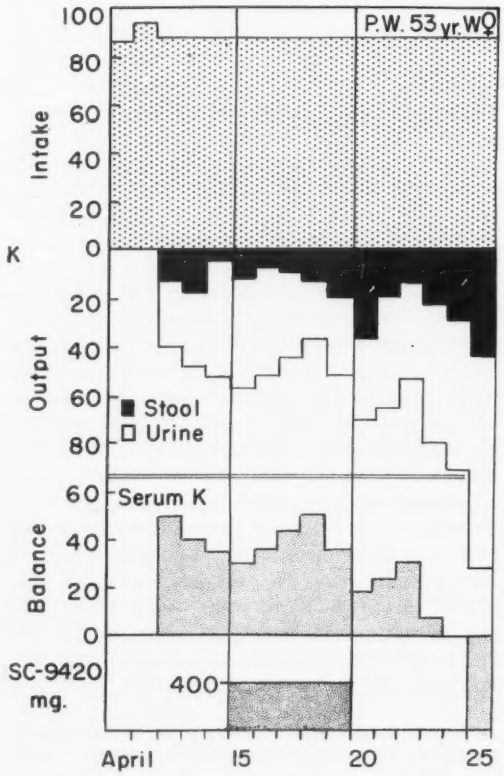

Figure 2

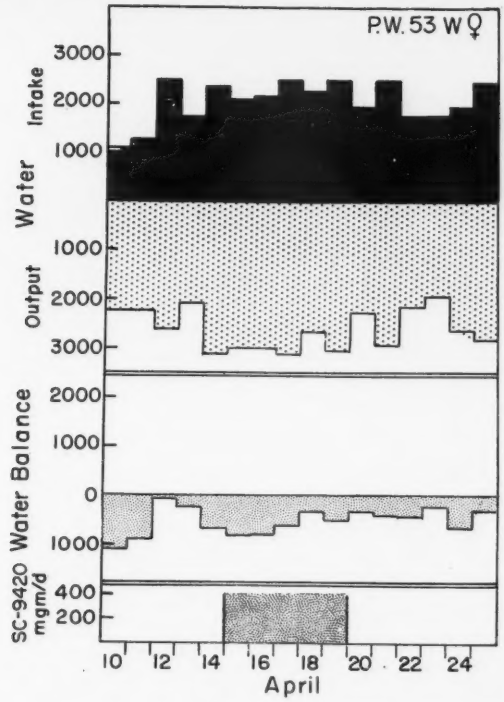

Figure 3

cause of the cataract. Mild nuchal rigidity was present. The remainder of the examination was not remarkable; there was no edema. The neurologic examination was normal except for the neck stiffness.

A spinal puncture was done showing grossly bloody fluid with an opening pressure of 240 mm.

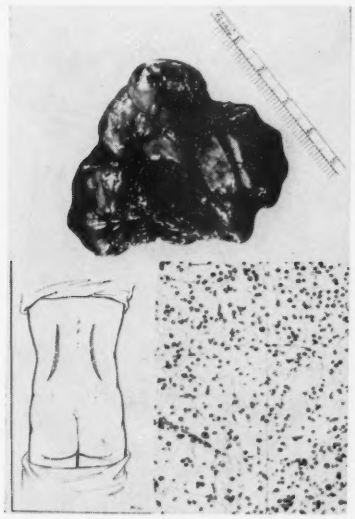

Figure 4

of spinal fluid and a closing pressure of 140 mm. She was placed at bed rest and given a 1400 calorie, 40 gram fat, 1600 milligram sodium diet. Laboratory evaluation revealed serum sodium, 143 mEq/L; potassium, 2.2 mEq/L; chloride, 95 mEq/L; CO_2, 38.2 mEq/L; calcium, 5.2 mEq/L; phosphorous, 1.8 mEq/L. Serum albumin was 3.58 grams per cent; globulin, 2.99 gm per cent; blood sugar 76 milligrams per cent. A 24-hour urine collection revealed sodium, eight mEq; potassium, 11 mEq; chloride, five mEq. The blood pH was 7.49. On the sixth hospital day she was placed on a regular diet with four grams of sodium chloride as supplement. After three days on this diet a 24-hour urine was collected and assayed for aldosterone, and 16.1 micrograms were found (normal 1-6 micrograms). An electroencephalogram showed a borderline tracing. The EKG showed a prolonged QT interval with prominent U waves suggestive of hypokalemia. The chest x-ray was not remarkable. IVP's showed normal functioning kidneys without obvious displacement.

TABLE I

P. W. AGE 53

Measured Values (± 5%)	
Body Weight	57.27 kg.
Total Body Water (TBW)	26.20 liters
% Body Weight	45.75
24 hr. Exchangeable Body K	1690 mEq
mEq/kg.	29.5
mEq/LTBW	64.5
Sodium Space	12.53 liters
% Body Weight	22.05
24 hr. Exchangeable Body Sodium	2762 mEq
mEq/kg.	48.2
Hematocrit	40.0
Blood Volume	3640 cc.
Red Cell Mass	1398 cc.
Plasma Volume	2242 cc.

TABLE II

Derived Values (± 10%)	
Lean Body Mass	35.79
% Body Weight	62.5
Body Fat	21.48
% Body Weight	37.5
Compositional Derangement (± 10%)	
Potassium	–434 mEq deficit
Sodium	+697 mEq excess
Intracellular	+289 mEq
Sodium Space	+238 mEq
Bone Sodium	+170 mEq

Because it was believed that the patient might well have primary aldosteronism, she was given the spirolactone, SC-9420, during a balance study. Data for sodium potassium and water balance is presented in Figures one to three.

Clinical Course

Throughout the remainder of her hospitalization she continued to feel well, with a diastolic pressure range between 90 and 110 mm. of mercury. There was no recurrence of cerebral hemorrhage. Following the study period she was discharged on a 1650 milligram sodium, 1400 calorie, 40 gram fat diet and 120 mEq of potassium by mouth daily. She was readmitted on May 15 at which time there was no change in her physical examination. Her blood pressure was 180/98. Chest, heart, and abdominal examinations were again within normal limites. A urinalysis and blood count were relatively unchanged. Serum sodium was 142 mEq/L; potassium, 2.6 mEq/L; chloride, 98 mEq/L; CO_2, 39.5 mEq/L. The electrocardiogram continued to show change consistent with hypokalemia. Sodium excretion ranged between four and ten milliequivalents per 24 hours. On May 20, under nitrous oxide and fluothane anesthesia, an adrenal exploration was undertaken. The right adrenal was exposed and an adenoma approximately 1.2 cm. in diameter was palpated in its mid-portion. The entire right adrenal gland was removed by individual ligation of the blood vessels

TABLE III

CASE NUMBER	DATE	AGE	SEX	POLYURIA	POLYDIPSIA	NOCTURIA	WEAKNESS	PARALYSIS	HEADACHE	CRAMPS	EDEMA	DURATION	BLOOD PRESSURE	E K G	I V P	Retro-Peritoneal Air Insufflation
1[1]	1955	34	♀	+	+	+	+	+				8 yr.	176/104	↓ K	N	N
2[2]	1955	33	♂	+	+	+	+			+		2 mo			N	N
3[3]	1956	39	♀				+					"yrs"	220/110	↓ K		
4[4]	1956	46	♀	+			+	+				4 yr.	220/115		N	N
5[5]	1956	32	♀	+	+		+						180/105		N	Tumor
6[6]	1956	43	♀				+					3 yr.	225/140	↓ K	N	N
7[7]	1956	32	♂		+		+						180/120			Tumor
8[8]	1954 1957	41	♀					+				4 yr.	180/110	↓ K LUH		Tumor
9[8]	1956	60	♀						+				180/110	↓ K LUH		N
10[9]	1957	44	♂		+		+					3 yr.	200/128	↓ K	N	Left Mass
11[9]	1957	63	♂		+	+	+		+			5 yr.	170/100	↓ K	N	N
12[9]	1957	42	♀	+	+		+			+		"yrs"	220/110	↓ K		Left Mass
13[10]	1957	40	♂	+			+					7 yr.	↑	↓ K		
14[11]	1957	26	♀	+			+					6 yr.	220/130	↓ K		
15[12]	1957	33	♀				+			+		4 yr.	250/100	IV Block	N	N
16[13]	1957	45	♀				+	+	+			6 yr.	200/100	↓ K LAD		
17[14]	1958	40	♂								+					
18[15]	1958	27	♂	+	+							1 yr.	260/160	LVH LVS	↓ Rt. Kidney	Mass
19[16]	1958	43	♀	+	+		+		+		+	4 yr.	170/100	↓ K		
20[17]	1958	47	♀				+					3 yr.	175/105	↓ K	N	N
21[18]	1958	34	♀									12 yr.	230/140	↓ K		
22[19]	1958	38	♂		+		+					3 yr.	175/120	↓ K	N	
23[20]	1958	49	♀										↑	↓ K		
24[21]	1959	45	♀	+	+							14 yr.		↓ K		
25[22]	1959	45	♀									5 yr.				Left Mass
26[22]	1959	50	♀				+				+	4 yr.		↓ K		Left Mass
27	1959	43	♀				+		+			18 yr.	210/120	↓ K	N	
28	1959	51	♀				+					7 yr.	220/110	↓ K	N	
29[23]	1956	17	♂		+	+			+				220/150	↓ K	N	Left Mass
30[15]	1958	13	♂		+	+						4 yr.	160/120			
31[24]	1956	32									+	1 yr.	160/105		N	N
32[25]	1959	52	♀													
33[26]	1957	40	♂	+		+						11 yr.	230/120	LVH		Left Mass
34[27]	1955	60	♂	+	+			+				8 mo		↓ K	N	Tumor

①Superscript denotes reference in bibliography; 1-28 adenomas, 29-32 hyperplasia, 33-34 carcinomas

TABLE IV

Case No.	*BUN mg. %*	*Urea*	*GFR ml/min.*	*RPF ml/min.*	*Max. Concentration*	*Urine pH*	*Blood pH*
1	33-38	*1	Creatinine = 125-170 liters/day		1.011		7.62
2							7.5
3					1.010		
4					↓		
5					1.010		7.57
6					Isosthenuria	impaired acidification	
7							7.59
8		58%	65 Creatinine		Isosthenuria		
9	35		65 Creatinine		1.016		
10	42	93-97%	120 Inulin	412			
11	34				1.011		7.5
12	21	60-80%					7.5
13					↓	impaired acidification	
14					1.012		
15					1.024		7.54 7.47
16			98 Creatinine		1.011	7.1-7.3	7.46
17							
18			108 Inulin		*2		
19		PSP 70% 2 hrs.			1.012		7.42 7.44
20	14-35	66%			1.020	impaired acidification	
21							
22						6.0-8.0	
23					↓		
24			73 Creatinine 60 Mannitol	350		7.65	
25							
26						alk.	
27	10.5	*3			1.014	7.5	
28	7.5					alk.	7.49
29		PSP 80% 2 hrs.	96 Creatinine		1.016	6.9-7.1	7.44
30		PSP 63%			1.014		
31					1.011		
32							
33	38	87	78 Creatinine		*4		
34							

*1-PSP
50%-15 min.
80%-2 hrs.

*2-1.010 H_2O
water deprivation
535 Mos. m/kg.

*3-34 Max.
PSP, 20.5-15 min.
61.5-1 hr.

*4-1.012
with pit.
540 mOsm/l.

TABLE V

Case No.	*Aldosterone (mcg/day)*	*17 Hydroxycorticoids (mg/day)*	*17 Ketosteroids (mg/day)*	*Other*
1		5.0	5.7	
2				
3				
4				
5	3-28			
6	8, 11, 28	40.35 21		
7		5.8	17.2	
8	↑	N	N	
9	N	N	N	
10	27.5 N 26		12	
11	48.5	10.6	4.5	
12	230 DCA equiv. (4 × N)			
13	38.3, 28.4 (N 5-23)	21, 16.4 (N 13-86)		Comp. B 0.82 (N 2.2-9)
14	28	3.5	N 7.5	
15				
16	9.6, 30.4, 9.2, 16.0, 22.0, 35.0		7.5	
17	60			
18	39-41 (N 5.8-11.1)	19		
19				
20	1.8-6.7 (N 3-7)			
21	↑			
22	19.8, 26 (N 3-9)		10	
23	32, 56, 105, 73, 47			
24	11-25 (N<12)	high N	low N	NoS, Tetrahydros N
25	80	N		11 = Oxysteroids N
26	24	N		11 = Oxysteroids N
27			11.2	11 = O, 16.8
28	16 (N<6)	4.9	5.8	
29	34 (N<8)			
30	8, 5, 5, 12, 33	5.5		
31	300	37	11	Comp. B 24 (N.08-.12) Hydrocortisone 1 (N.04-.26)
32			N	
33	20, 20, 30 (N 2)	29, 25, 33		
34	12 DCA equiv. (r = 4.8)			

N = Normal

medially. The cut section revealed a firm, well circumscribed cortical adenoma with a satellite adenoma approximately four mm. in diameter. The incision was closed, and the patient was returned to the recovery room.

Following surgery the serum potassium gradually rose, and at the time of discharge the serum electrolytes were: sodium, 134 mEq/L; potassium, 4.7 mEq/L; chloride, 98 mEq/L; CO_2, 25.2 mEq/L. Urinary electrolyte excretion of sodium increased on successive days to 20, 106 and 66 mEq per 24 hours. Her 48-hour postoperative balance is shown in Figure one.

Preoperative data on the patient's total body sodium, potassium and water are shown in Tables one and two. She has remained well since surgery, her blood pressure dropping to 130-140/80-90. At the time of the postoperative follow-up in October, 1959, the serum sodium was 138 mEq/L; potassium, 4.7 mEq/L; chloride, 98 mEq/L; and CO_2, 23.8 mEq/L. The tumor and incision are shown in Figure four.

Experimental Methods

During the study period the patient received the same diet each day. A duplicate tray was analyzed and found to contain 94 mEq of potassium and 27 mEq of sodium. Assay was performed by homogenizing the duplicate diet with de-ionized water; triplicate aliquots were digested with .75 normal nitric acid, filtered, and the supernate analyzed for sodium and potassium utilizing a Coleman Model 21, flame photometer attached to a Model 14 Universal spectrophotometer for reading. Serum and urinary electrolytes were determined utilizing the same machine by standard methods. Stool specimens were collected, weighed and frozen until assay. Samples were homogenized and weighed aliquots were assayed after digestion with nitric acid as described in the Coleman Manual D-248-B, Coleman Instrument Company. Blood pH was determined on heparinized finger-tip blood with a Sanz microelectrode (type EA-518) attached to a Cambridge model research pH meter. A Gebruder-Haake type F constant temperature bath was used to maintain electrode temperature at 38 degrees centrigrade. Aldosterone assay was performed by Dr. Robert Bolinger, utilizing methylene chloride as the extracting medium. The samples were chromatographed in the Bush C system and the aldosterone was estimated utilizing Gornall's color method with dinitrophenylhydrazine. Body water, sodium and potassium were determined by Dr. Paul Schloerb using sodium 23, potassium 42 and deuterium oxide dilution techniques.

Discussion

Thirty-two cases of aldosterone excess collected from the literature[1-27] are tabulated with the two cases presented here in Tables three, four, and five. Twenty-eight of these patients had adrenal adenomas of which seven were on the right and 19 were on the left; two were not reported as to location. Four had hyperplasia alone and two had adrenal carcinomas. The more common complaints are graphed in Figure five. Four patients had had some degree of edema.

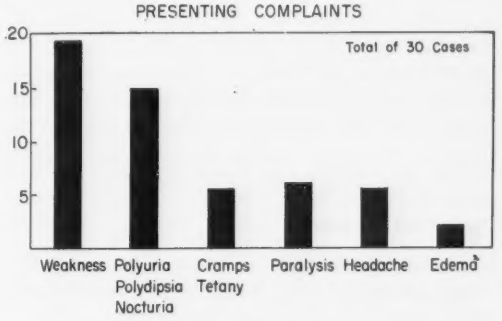

Figure 5

All patients had hypertension and most showed electrocardiogram changes consistent with hypokalemia. Intravenous pyelograms did not contribute to the diagnosis whereas retroperitoneal air study frequently demonstrated a tumor mass (11 of 20). All showed at least one serum potassium that was abnormally low, and many showed increased sodium and increased CO_2 content.

Hyposthenuria was a consistent finding as was impaired urinary acidification with excretion of an alkaline urine. Other aspects of renal functions are noted in Table four.

Urine steroid excretion data are tabulated in Table five. Because of considerable variation between laboratories in aldosterone assays, normal values are given for each report where known. Consistent elevation in aldosterone excretion is noted, with the majority showing 17-hydroxy and 17-ketosteroid excretion in the normal range. Unusual in this respect were cases 24 and 31.

Left-sided tumors were almost three times as frequent as those on the right side. No extra-adrenal lesions have been reported to date. With this in mind it would seem best to use the posterior approach because of its technical facility as compared to abdominal exploration.

Effect of Spirolactones

Salass, Mattox, and Powers, and Kistler, Shelley, and Frawlery, have reported on the use of a spirolactone in patients with primary aldosteronism. The

(Continued on page 188)

Chronic Gastric Volvulus

Symptoms of Epigastric Pain and Emesis

CREIGHTON A. HARDIN, M.D.; *and*
COLVIN H. AGNEW, M.D., *Kansas City*

GASTRIC VOLVULUS IS a rare condition capable of producing an acute abdominal crisis. Berti recognized and described this condition. Berg treated such a case by operation, and Rosselet described its roentgen appearance. A review of the literature by Gottlieb, Lefferts, and Beranbaum added 20 cases.

Acute or Chronic

Gastric volvulus may be either acute or chronic. Acute gastric volvulus should be considered a surgical emergency. Volvulus proves fatal unless a clinical awareness exists, and a prompt diagnosis is made, followed by proper surgical treatment. Borchard presented a clinical triad of symptoms consisting of vigorous vomiting without relief, epigastric pain with radiation to the back and inability to pass a stomach tube.

By definition acute gastric volvulus should be reserved for those patients presenting with an acute unrelenting obstruction. Hazards of acute volvulus are ischemia of the stomach with gangrene and aspiration of vomitus. Successful surgical treatment of acute gastric volvulus in a 22-month old infant has been reported by Goldberg and Smith while most of the cases described in the literature have been in adults. The collective mortality of his reviewed series of 48 cases was 60 per cent.

Chronic or intermittent gastric volvulus is more common than the acute form, and does not bear such an immediate serious prognosis. Clinically the symptoms of epigastric pain and emesis are periodic. The rotational obstruction is intermittent and when reduced a stomach tube may be passed. A more descriptive term of organo-axial rotation has been suggested for chronic gastric volvulus.

Case Report

A 58-year-old white man was admitted to the University of Kansas Medical Center on December 27, complaining of epigastric pain radiating posteriorly between his shoulders. The onset of pain abruptly began soon after meals, and was so intense as to double him up. Severe vomiting gave relief to these painful attacks. Present episodes began about two months before admission, and occurred every three to four days. There was no history of jaundice, hematemesis, or melena. A past history of seven years was replete with repeated bouts of pain similar to those on admission. Yearly barium studies of the stomach failed to demonstrate a gastric or duodenal ulcer. Non-specific findings of a hyperirritable duodenal bulb and delayed gastric emptying were described by the radiologist. Gallbladder series were done on two occasions and reported as normal. Since 1955 the patient had been treated medically with a low fat bland diet, antispasmodics, and antiacids. Relief at best on such a program was intermittent,

A case of chronic intermittent gastric volvulus successfully treated by gastric resection is presented. The clinical symptoms, important roentgen findings, and treatment is reviewed.

Figure 1. Normal appearing stomach in February 1956.

From the Departments of Surgery and Radiology, University of Kansas Medical Center, Kansas City, Kansas.

punctuated every three to four months by recurrent bouts of acute pain and vomiting. Studies of gastric acidity with histamine stimulation on two occasions were normal. Physical examination was essentially negative except for epigastric tenderness and moderate distension of the upper abdomen.

A blood count and urinalysis were normal. An electrocardiogram was normal. Serum amylase and leucine amino pepidase values were normal.

Radiographic and fluoroscopic studies with barium showed an abnormality present in the mid-portion of the body of the stomach. The stomach, visualized in the right anterior and frontal views, showed the proximal one-half of the stomach rotated on itself. The proximal stomach had undergone organo-axial rotation producing a partial obstruction. Two levels of layered air and fluid were seen in the obstructed stomach *(Figure 2)*. A repeat barium study 24 hours after continuous gastric suction showed the obstructing rotation reduced *(Figure 3)*. The gastric emptying was delayed but considerable retained fluid was present. No hiatal hernia could be demonstrated.

Preparation for surgery consisted of continuous gastric suction and intramuscular atropine every six hours. This regimen was carried out for 48 hours, and provided symptomatic relief.

The patient was explored under general anesthesia on the third hospital day. The liver, gallbladder, and intestines were normal. There were no ulcers in the duodenum or stomach. The organo-axial rotation of the proximal stomach could be reduplicated manually. A deficiency in the mesenteric attachment along the greater curvature of the stomach beginning at the lower pole of the spleen allowed the rotation to take place. A 50 per cent Billroth I gastrectomy and vagotomy was done. The postoperative course was uneventful, and the patient was discharged seven days after surgery.

Examination of the excised segment of stomach showed many acute superficial scattered ulcerations probably secondary to the intermittent partial obstruction.

Discussion

A useful topographical classification of volvulus has been presented by von Haberer and Singleton.

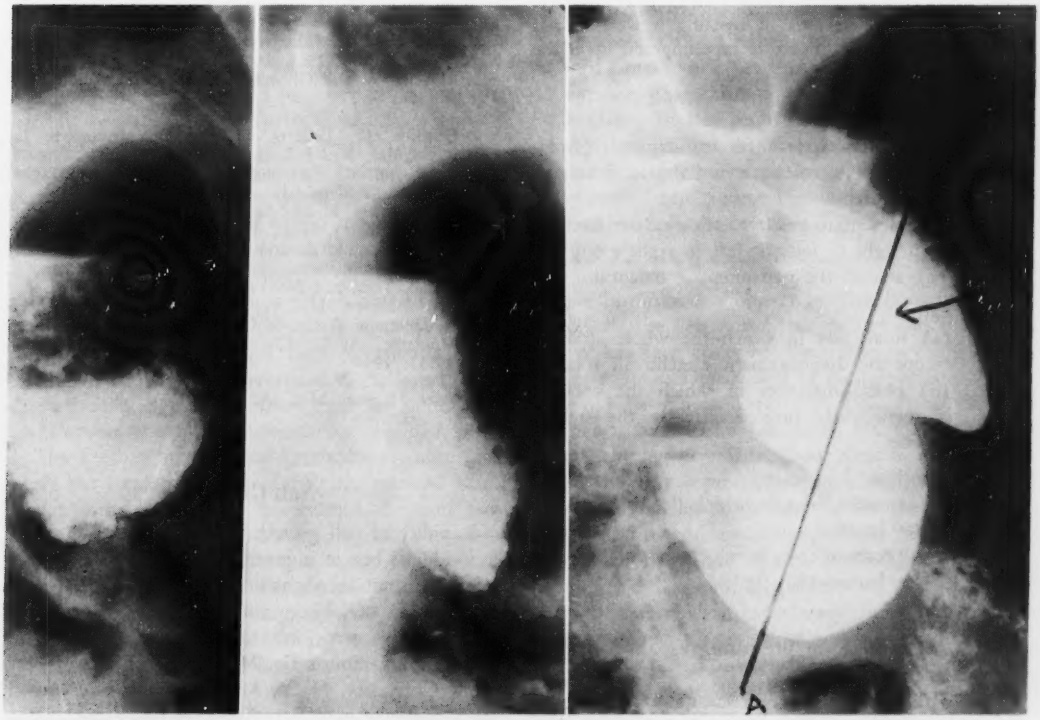

Figure 2A. Initial barium sulfate administration demonstrates the double fluid level. The barium sulfate was temporarily obstructed at the area of twisting. As additional barium was given (B) this area relaxed to outline the antrum.

Figure 2C. The filled stomach with the axis of rotation (A-B) showing the cardia rotating from left to right. No diaphragmatic hernia could be demonstrated.

Figure 3. The filled stomach viewed from the left anterior oblique. The area of twisting is well shown. The air-filled splenic flexure is superimposed upon the body of the stomach.

I. Type
(a) organo-axial: infra- or supracolic rotation of the stomach around the long axis of the stomach
(b) mesentero-axial: rotation of the stomach from right to left, or left to right along the long axis of the gastrohepatic omentum.

II. Extent
(a) total-cases in which the whole stomach except the diaphragmatic attachment rotates
(b) partial-instances in which the rotation is segmentally limited, usually the pyloric portion.

III. Direction
(a) anterior-cases in which the rotating part passes forward
(b) posterior-cases in which the rotating part passes backward.

IV. Severity
(a) acute-form presenting as an abdominal emergency
(b) chronic-form presenting with constant or recurrent milder symptoms or symptomless.

To understand the process of gastric volvulus, a certain atony or lengthening of peritoneal fixations must occur in the gastrosplenic, gastrophrenic, hepatogastric, and gastroduodenal ligaments with some degree of ptosis of the stomach. The omental fixation of the transverse colon is also a contributory factor because the colon may rotate with the stomach. Secondary contributory factors, listed by Payer, are diaphragmatic hernia or eventration, benign and malignant tumors, peptic ulcers, and displacement by neighboring organs.

A clinical suspicion of the triad of symptoms should be followed by confirmatory x-ray examination. Supine and erect abdomen films may complete the diagnosis. In acute complete volvulus there is no passage of barium sulphate. Unusual amounts of colonic gas have been noted in the transverse colon and splenic flexures. A double fluid level may be seen with barium swallow in the incomplete partial volvulus. When more barium is given and films are taken in the erect position the direction of torsion becomes more apparent. Recumbent films may be complementary but fail to yield information leading to the diagnosis.

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Nail Growth

Rapidity of nail growth varies considerably among individuals, but in a given person generally is relatviely constant throughout life. Growth is increased, however, in nail biters and during pregnancy; it is decreased by acute infections, chronic disease and malnutrition, reports Dr. Maarten S. Sibinga of New York University, N. Y. Measles arrests nail growth for variable periods. Retardation of nail growth sometimes accompanies the common cold, the period of elevated temperature of mumps and infections severe enough to cause weight loss.—*Modern Medicine,* Nov. 15, 1959.

K.U.M.C. Cancer Registry

A Record of Cancer Cases Over the Past Twelve Years

ROBERT E. STOWELL, M.D., ***Washington, D. C.***

The objectives and plan of operation of the tumor registry and follow-up service at the University of Kansas Medical Center are presented. Data on 9,823 cancer cases have been coded in the registry in the past 12 years. The registry has aided in the improvement of service to cancer patients, statistical research, and cancer teaching for the State of Kansas.

IN 1949 THE TUMOR registry and follow-up service was established to serve the University of Kansas Medical Center. Cancer cases for 1947 and 1948 were subsequently added to the registry. For a variety of reasons it seems desirable to report on the results of its first 12 years' operation. An account of this registry has not been previously published although it has been discussed at national cancer meetings and has supplied useful information on its operation to numerous other institutions establishing registries.

Objectives of Registry

A university medical center exists for teaching, patient services and research, and a tumor registry and follow-up service at a medical center should serve all these needs. In establishing any tumor registry, it is important to ascertain the specific objectives and the available facilities which can be used to meet these needs. The optimal type of registry for different situations will vary greatly. In a university medical center, the purposes include: to obtain factual information on the incidence and results of therapy of all cancer cases within the institution; to aid the patient, physicians, researchers, and medical students; and to improve patient care, research and teaching. Generally, such registries should include only simple basic data which will serve as a guide to finding the cases on which more detailed research will be done. The accuracy of data collected is of much greater significance than the total number of cases or the amount of information obtained.

The keeping of systematic records on cancer patients has increased greatly during the past 20 years. The requirements of the American College of Surgeons for approval of a cancer program encourage more hospitals to establish tumor registries. Haenszel and Hon have discussed the various statistical approaches to cancer including analysis of mortality data, retrospective studies, forward study of cohorts, morbidity surveys, screening of populations, and cancer registers. They discuss the relative merits of registries maintained by state departments of health and by other institutions. All states and all hospitals do not need cancer registries. The establishment of a registry is an expensive undertaking which must be maintained for many years to become valuable. The critical question is whether such expenditures are more warranted than other utilizations.

Plan of Operation

The registry at the University of Kansas has cooperated closely with that of the Kansas State Board of Health, although objectives have been quite different. At the University, the registry and follow-up service has been under the general supervision of the chairman of its Department of Pathology and Oncology and its cancer committee. Fortunately, several physicians have had a substantial interest in the success of the registry. Throughout most of its existence one unusually competent tumor registry librarian with two secretarial assistants has handled routine operational details and maintained desired liaison with the record room and clinical staff. With a unified central record system, all patients on whom a diagnosis of cancer has been made have their charts checked by registry personnel when they are returned for filing to the record room. Charts on which cancer has been diagnosed are stamped on the cover sheet with a red star for quick future identification.

Pertinent data are kept on IBM cards. The basic, nonscientific information is obtained on coding sheets by the tumor registry secretary. The initial medical data are recorded independently by both the registry

From the Department of Pathology and Oncology, University of Kansas Medical Center. Registry is supported by a grant from the American Cancer Society, Kansas Division, and grant CT495 from the National Cancer Institute, Public Health Service. Present address of author is Armed Forces Institute of Pathology, Washington 25, D. C.

secretary and the clinical resident on the service. Duplicate IBM cards are made from each source, verified and pertinent information such as the diagnosis typed on the face of the card for convenient reference. There is good relationship with staff as well as referring physicians in obtaining follow-up information at six months intervals for the first five years and annually thereafter. If information needed is not available on the patient's chart, an autotypist is used to automatically prepare original copy, individualized follow-up letters to the patient or referring physician. The success of follow-up on the first 10,000 cases is better than 98 per cent. A separate file card marked for month of follow-up is kept and a new IBM card is punched to provide the latest information on each case. Tumor classification is made by a slightly modified standard nomenclature of diseases.[8]

About a sixth of the cases of cancer in this state at some time enter the University of Kansas Medical Center and are incorporated in this registry, which is one of about 30 institutional registries in Kansas. The central registry of the State Board of Health is advised of all new cases and furnished a tabulated annual report from which information can be incorporated with that of other institutional registries. The Board of Health gives some assistance in follow-up information including copies of death certificates.

Results

The patients appreciate the interest shown in them during follow-up and are encouraged to regularly see their physicians. The registry fosters better patient treatment. The facilities of the registry are used by faculty, residents and students for obtaining information and for doing research on symptomatology, diagnosis, treatment and prognosis of cancer patients. Recently for example, epidemiological studies on cancer of the lung and stomach have been aided. The IBM facilities are also used for a variety of other statistical research problems.

Between January 1947 and December 1958, 9,160 cases were registered, and other surviving previous cases were added to comprise 9,823. Age distribution for main sites is shown in *Table 1*. Some information as to percentage distribution of site, stage and microscopic proof of diagnosis is given in *Table 2*. The percentage of localized tumors was less than one per cent for lymphatic and hematopoietic tissues,

TABLE 2

PERCENTAGE DISTRIBUTION OF 9,823 CANCER CASES BY SITE, STAGE OF DISEASE AND MICROSCOPIC PROOF OF DIAGNOSIS

Site	*% Total Cases*	*% Localized*	*% Microscopic Proof*
Buccal cavity and pharynx ..	6.0	45.2	96.9
Digestive organs	15.8	21.0	94.5
Respiratory system	9.5	15.1	91.9
Breast	10.0	34.5	96.2
Female genital organs	13.7	33.1	98.7
Male genital organs	7.5	20.8	86.2
Urinary organs	4.9	43.7	94.6
Skin	8.8	73.6	91.9
Brain and nervous system ..	4.0	47.6	93.2
Lymphatic and hematopoietic	12.2	.3	97.1
Other and unspecified	7.6	22.6	90.6
Per Cent Total.....	100.0	29.3	94.3

TABLE 1

CANCER CASES REPORTED BY SITE AND AGE GROUP

		Age Group															
Site	*Total*	*0*	*5*	*10*	*15*	*20*	*25*	*30*	*35*	*40*	*45*	*50*	*55*	*60*	*65*	*70 and Over*	*Not Stated*
Buccal cavity and pharynx	588	1	2	6	7	8	11	11	20	22	36	40	75	66	95	187	1
Digestive organs	1552	7	1	2	4	8	12	29	36	46	82	112	173	249	287	504	0
Respiratory system	940	3	0	2	3	2	3	11	14	48	90	131	166	160	165	142	0
Breast	989	0	0	0	0	0	12	24	53	88	131	131	111	138	130	168	3
Female genital organs ..	1341	1	0	1	4	12	35	78	94	130	166	188	182	165	131	153	1
Male genital organs	739	2	0	0	5	0	14	9	7	6	9	18	39	61	149	419	1
Urinary organs	481	17	3	0	0	1	8	4	8	15	25	40	55	72	85	148	0
Skin	861	0	0	0	4	1	10	15	24	26	37	57	73	108	149	354	3
Brain and nervous system	397	27	33	21	15	17	12	20	26	29	32	50	48	34	21	12	0
Lymphatic and hematopoietic	1188	93	55	34	45	35	28	43	39	62	94	118	103	110	142	185	2
Other and unspecified ..	747	44	13	23	23	24	19	27	36	35	60	55	78	97	84	128	1
Total	9823	195	107	89	110	108	164	271	357	507	762	940	1103	1260	1438	2400	12

and 74 per cent for skin. Nearly 95 per cent of the diagnosis were confirmed microscopically. The percentage of microscopic proof of diagnosis was higher than obtained in many registries.[4]

OCCUPATION AND DIAGNOSIS

Indoor work was performed by 6,680 and 1,102 were farmers. Slightly less than four per cent of patients were unaware of cancer symptoms, of which

TABLE 3

STAGE OF DISEASE OF REGISTERED CASES BY YEAR OF FIRST DIAGNOSIS, 1947-1958

Year	Number of Patients	Per Cent of Total				
		LOCALIZED	REGIONAL INVOLVEMENT	REGIONAL NODES INVOLVED	DISTANT METASTASIS	STAGE NOT RECORDED
1947	427	36.1	22.2	15.0	12.2	14.5
1948	511	27.8	22.7	17.8	12.5	19.2
1949	609	32.5	21.2	16.3	12.0	18.0
1950	795	35.6	18.1	18.0	7.9	20.4
1951	848	33.6	17.7	14.9	12.5	21.3
1952	832	32.5	18.5	15.0	12.1	21.9
1953	860	27.2	22.8	15.7	13.1	21.2
1954	830	29.7	21.9	14.1	15.4	18.9
1955	846	26.4	21.0	14.3	18.8	19.5
1956	834	24.3	21.1	15.7	16.1	22.8
1957	865	30.2	22.0	13.5	13.6	20.7
1958	903	28.8	21.1	15.8	11.8	22.5
Total	9160	30.1	20.8	15.4	13.3	20.4

TABLE 4

TYPE OF TREATMENT GIVEN DURING FIRST ADMISSION IN REGISTERED CANCER CASES BY SITE, 1947-1958

Selected Sites	Number of Patients	Therapy							
		SURGERY	RADIATION	SURGERY AND RADIATION	CHEMOTHERAPY: ALONE	CHEMOTHERAPY: WITH SURGERY	CHEMOTHERAPY: WITH SURGERY AND RADIATION	CHEMOTHERAPY: WITH RADIATION	None
Buccal cavity	537	39.8	36.3	18.1	0.2	0.7	0.2	0.6	4.1
Digestive organs	1516	68.8	1.9	2.4	1.9	2.4	0.1	0.3	22.2
Respiratory system	926	33.7	19.0	5.7	5.6	1.2	0.0	4.1	30.7
Breast	813	44.5	3.1	36.3	0.6	2.8	8.9	2.0	1.8
Female genital organs	1191	12.8	57.3	22.4	0.5	0.4	1.2	2.1	3.3
Male genital organs	722	14.1	0.8	5.1	8.1	65.9	2.2	0.3	3.5
Urinary organs	459	56.6	7.6	16.8	2.6	2.0	1.3	0.2	12.9
Skin	747	65.6	16.1	15.4	0.1	1.2	0.4	0.1	1.1
Brain and nervous system	378	45.5	10.6	22.2	0.8	0.0	0.3	0.3	20.3
Lymphatic and hematopoietic systems	1163	1.5	23.2	3.8	46.5	0.4	0.9	14.6	9.1
Unspecified	708	32.3	19.1	18.8	5.2	0.8	0.6	3.0	20.2
Total	9160	36.6	18.7	13.5	8.1	6.4	1.4	3.1	12.2

2.5 per cent were recognized as a result of routine examination; in 1 per cent cancer was found as a result of an operation or other medical procedure not undertaken because of a diagnosis of cancer, and 0.3 per cent were found as a result of an exfoliative smear made as a routine screening procedure. Exfoliative cytologic diagnosis is not as widely used in Kansas as in many other areas, although its use is increasing.

TABLE 5

ONE, THREE AND FIVE-YEAR SURVIVAL RATES FOR SELECTED SITES OF CANCER BY STAGE, 1947-1953

Site and Stage of Disease	*Number of Patients*	*Per Cent Surviving* 1 YEAR	3 YEARS	5 YEARS
Buccal Cavity				
Localized	167	88.0	67.1	56.3
Regional involvement	72	76.4	51.4	31.9
Node involvement	59	54.2	18.6	13.6
Distant metastasis	8	25.0	12.5	0.0
Stage not recorded	20	85.0	40.0	30.0
Digestive System				
Localized	202	75.2	58.9	43.1
Regional involvement	144	51.4	29.2	22.2
Node involvement	192	44.8	19.3	14.6
Distant metastasis	217	12.0	0.9	0.0
Stage not recorded	61	62.3	27.9	16.4
Respiratory System				
Localized	61	68.9	42.6	31.1
Regional involvement	151	42.4	24.5	18.5
Node involvement	130	31.5	9.2	6.9
Distant metastasis	53	3.9	0.0	0.0
Stage not recorded	44	27.3	15.9	11.4
Breast				
Localized	179	95.0	83.2	66.5
Regional involvement	22	100.0	86.4	68.2
Node involvement	208	81.7	56.2	42.8
Distant metastasis	22	77.3	4.5	0.0
Stage not recorded	70	80.0	70.0	48.6
Female Genital Organs				
Localized	231	92.2	78.4	70.1
Regional involvement	185	79.5	55.7	43.8
Node involvement	103	68.0	40.8	32.0
Distant metastasis	113	38.9	12.4	8.8
Stage not recorded	80	82.5	53.8	37.5
Male Genital Organs				
Localized	114	83.3	52.6	43.0
Regional involvement	170	74.1	51.2	33.5
Node involvement	11	81.8	9.1	9.1
Distant metastasis	40	45.0	30.0	12.5
Stage not recorded	29	79.3	48.3	34.5
Urinary Organs				
Localized	115	80.9	58.3	47.8
Regional involvement	76	51.3	19.7	11.8
Node involvement	8	12.5	12.5	12.5
Distant metastasis	32	25.0	3.1	3.1
Stage not recorded	10	50.0	40.0	40.0
Skin				
Localized	336	92.0	73.2	61.3
Regional involvement	49	77.6	53.1	38.8
Node involvement	17	52.9	23.5	17.6
Distant metastasis	5	40.0	0.0	0.0
Stage not recorded	16	100.0	81.2	56.2

It is of interest that it was claimed that there was an elapse of less than six days in 30 per cent of cases from the time of onset of symptoms to the first visit to a physician, in 35 per cent of cases from first visit to a doctor to date of definitive diagnosis, and in over 80 per cent from definitive diagnosis to date of first treatment. Similarly the figures for less than 28 days are 40, 60, and 95 per cent respectively. If correct, this would represent relatively prompt visits of patients, to physicians who made early diagnosis and gave prompt treatment.

TUMOR STAGE AT ORIGINAL DIAGNOSIS

At the time of original diagnosis, the stage of malignancy was localized in only 3,108 cases, invasion into surrounding tissue in 1,994, metastases to regional lymph nodes in 1,605, generalized in 1,618, and unknown in 1,604 cases. The stage of the tumors when first seen at the medical center is shown by years in *Table 3*. There is no significant trend over these 12 years toward a higher or lower percentage of patients with localized or metastatic cancer. Such data on principally referred patients are a selected sample which might not reflect improved earlier diagnosis within the area. Other studies of states have shown an increasing incidence of diagnosis of localized tumors.[4]

MULTIPLE TUMORS

As to the number of cases with more than one tumor of any type, there were two tumors in 310 cases, three in 32, and four to ten in 17 cases. In 75 patients there were two identical multiple tumors, in ten cases three, and in 12 cases four or five identical tumors. At last follow-up there were 30.2 per cent of patients symptom free of their cancer, 5.3 per cent ill with symptoms of cancer, 0.2 per cent alive but condition unknown; 54.7 per cent had died presumably of their cancer, 8.6 per cent died apparently of a cause other than the cancer coded, and 0.8 per cent died of causes unknown.

TREATMENT

The types of treatment given during their first admission to the medical center for groups of tumors are given in *Table 4*. One-fifth and one-third respectively of cases of tumors of the digestive and respiratory organs received no treatment. Surgery alone was the principal initial treatment of all groups of malignant tumors except those of the female genital system (radiation), male genital system

(Continued on page 180)

Special Speech Education

Remedial Speech and Hearing Instruction in Kansas

RALPH L. SHELTON, JR., Ph.D., ***Kansas City***

RECENT ARTICLES IN THE JOURNAL OF THE KANSAS MEDICAL SOCIETY suggest that Kansas physicians might be interested in knowing more about special educational procedures currently available to some Kansas residents who have faulty speech or hearing. These services, which are available in many of the universities and public schools in the state, involve the application of learning principles[5, 9] in teaching persons more acceptable speech patterns or how to use residual hearing more effectively.

Trained Personnel

The persons who provide this instruction have been variously termed speech correctionists, remedial speech instructors, speech therapists, speech pathologists, and audiologists. These terms partially reflect differences in professional training, and the latter two titles are reserved by many people for specialists holding doctorate degrees (Ph.D., Ed.D., or Sc.D.); at least 14 such persons are currently employed in Kansas. The speech pathologist is skilled in the appraisal of speech deficiencies and in their remediation or in research into speech and related subjects. The audiologist is skilled in the measurement of hearing as well as in educational procedures or research.

Speech and Hearing Association

Persons engaged in speech and hearing education are represented by the American Speech and Hearing Association, a professional organization founded in 1925. Members of the Association honor a comprehensive code of ethics. This group now publishes three journals including the *Journal of Speech and Hearing Disorders* and the *Journal of Speech and Hearing Research* which contain literature of a quality appropriate to the best traditions of laboratory research. With the development of speech and hearing as an independent but responsible profession has gone the discovery of new knowledge about speech and the speech learning process.

While most speech and hearing work in this country is done in university speech departments and in public schools, some instruction is offered in other settings including medical centers. Regardless of where the service is provided, the client's speech or hearing is compared with established norms, environmental etiological factors continuing to effect speech are identified and altered when possible, and lessons are planned to correct the speech. Many speech and hearing specialists require that their clients be examined by a physician before they undertake evaluation or training.[7] Developmental and other factors known to the physician may be related to some speech defects.

Research Setting

Perhaps the greatest cooperation between speech and hearing specialists and members of the medical profession has developed in research settings. Physicians have contributed to research projects and scientific reports formulated by speech and hearing personnel,[3, 10] and members of each group have cooperated in investigations into the anatomical-physiological bases of speech.[2, 11, 12]

Some of the special educational procedures currently available to Kansas persons who have faulty speech or hearing are discussed.

Five to Ten Per Cent

The high incidence of speech disability—five to ten per cent of the school children have speech defects serious enough to require instruction[6]—combined with a scarcity of remedial speech instructors has resulted in the hiring of some inadequately trained persons and corresponding development of conflict between such persons and members of other professions. However, it is more common for persons engaged in remedial speech and hearing work to hold advanced degrees. College graduation is required for membership in the American Speech and Hearing Association, and 50 per cent of the members held master's degrees. An additional 28 per cent have received their doctorates. The medical practitioner may find it helpful to refer his patients who present speech or hearing problems to the uni-

From the Department of Hearing and Speech of the University of Kansas Medical Center, Kansas City, Kansas.

versity speech and hearing centers or to some public school districts for evaluation and instruction.*

Handicaps Amenable to Training

Speech handicaps amenable to training include stuttering, some voice problems, delayed speech or language development, and speech problems associated with hearing loss, cerebral palsy, cleft palate, and other physical disabilities. Remedial speech and hearing instructors may choose to specialize and thus not undertake work with persons presenting certain of these problems. However, any qualified instructor can conduct training for persons with the most prevalent speech defect, faulty articulation. Articulation defects include the omission or distortion of sounds or the substitution of one sound for another.

In conclusion, it is emphasized that procedures of remedial speech instruction are founded on learning principles which were established by observation of organisms' behavior in experimental situations. Infrequent use is made of the theories of motor learning which are fundamental to physical therapy.[4]

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* The American Speech and Hearing Association periodically publishes a directory describing the education and employment of each member as well as the certification they hold within the Association. In 1958, 74 members worked in Kansas. Information regarding speech and hearing services may be obtained through the speech departments of various Kansas universities and also from James McLean who is state supervisor of speech and hearing services in the public schools. He may be contacted at the Division of Special Education in the State House, Topeka.

Cancer Registry

(Continued from page 178)

(surgery and chemotherapy) and those of the lymphatic and hematopoietic system. Of this latter group, 63 per cent had chemotherapy alone or in some combination, and 42 per cent had radiation in some form. In the earlier years of this period, chemotherapy was not used as much as recently.

Survival Rates

Somewhat more detailed information as to survival rates for some selected sites of cancer is given in *Table 5*. Patients with tumors of the respiratory tract had low survivals. The survival rates are low for most tumors with distant metastases. A third or more of the patients with lymph node metastases from cancer of the female genital organs and breast survived five years or more. The survival figures for breast were better than for skin tumors; many of the latter were complicated when first admitted. Further information can be obtained from the annual reports of the registry or by consulting the tumor registry itself.

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Oral Cancer Increases in Women

Oral cancer is on the increase among women, according to a study of the records of the Cook County Hospital (Chicago) and the Research and Educational Hospitals of the University of Illinois. In 1930 the ratio of women to men for oral malignancy was as follows: carcinoma of the lip, 1 to 16.2; floor of the mouth, 1 to 18.8; of the buccal mucosa, 1 to 8.5; of the esophagus, 1 to 4.1. In the period 1953 to 1957 at Cook County Hospital there were 46 women and 210 men patients with cancer of the month, a ratio of 1 to 4.56. At the Research and Educational Hospitals the incidence of oral cancer in 1944-48 was in the ratio of 1 to 10; in 1954-58 the ratio of women to men was 1 to 4.71. "This increased incidence in women is associated with an increasing use of tobacco by women and suggests a causal relationship. A long duration of exposure to the use of tobacco prior to onset of symptoms is a consistent finding," Drs. Walter W. Dalitsch and Sunder J. Vazirani concluded. —*American Journal of Surgery*, December, 1959.

Pain in the Legs, Fever, Chills, Splenomegaly, and Hypertension

Case Presentation

A 38-YEAR-OLD WHITE man was admitted to KUMC on August 3, 1957 complaining of pain and weakness in both legs for about two weeks. The pain migrated from his legs to his back and testicles, and he had some difficulty in walking. On July 25 his blood pressure was 142/82, and his temperature was normal. On July 30 he had fever and chills, and he was hospitalized. At that time his blood pressure was 130/75; temperature, 100.6 degrees; pulse, 89 per minute; respiratory rate, 22.

His past history and family history were noncontributory.

PHYSICAL EXAMINATION

When examined at KUMC the patient was found to be a well developed, well nourished man who was pale and appeared to be acutely ill. His blood pressure was 136/84; pulse, 82 per minute and regular; temperature, 99 degrees; respiratory rate, 20. There was a grade II rasping systolic murmur at the aortic area which was not transmitted. The liver was palpable at the right costal margin, and the spleen was palpated 5 cm. below the left costal margin. There was a yellowish tint to his palms and to the soles of his feet which were cool to the touch. The nail beds were cyanotic. The femoral artery pulses were of two plus intensity; the dorsalis pedis and posterior tibial pulses were only one plus. There was no evidence of varices of the lower extremities.

LABORATORY

The specific gravity of the urine varied from 1.010 to 1.029 with 10 to 20 pus cells and 2 to 3 red blood cells per high power field, 1 to 2 plus albumin, and a few motile bacteria. On admission the red count was 4,950,000 and the hemoglobin was 13.6 gm. There was moderate anisocytosis with normal shape and color. The white count was 60,315 with two per cent polymorphonuclears (two per cent filamented), eight per cent lymphocytes and 90 per cent immature mononuclear cells and blasts. The total white count subsequently gradually increased to 122,500 at the time of death, but there was no increase in the number of mature polymorphonuclears. A platelet count on admission was 70,000 and varied thereafter from 16,000 to 45,000. A Bence-Jones protein test was negative.

HOSPITAL COURSE

On admission the patient complained of severe pain in the calves of his legs and paresthesias of his feet. The nail beds became progressively more cyanotic, and the skin temperature gradually decreased. Vasodilating agents were not effective. On August 14 the femoral pulses, dorsalis pedis and posterior tibial pulses were completely absent. There was marked elevation pallor and dependent cyanosis, and his feet and legs were cold to the touch. On August 15 he developed nausea, vomiting, and severe pain in the lower abdomen, buttocks, and testicles. At that time his blood pressure was 180/100. On August 19, after the administration of a fibrinolytic agent, the pain in the extremities, testicles and sacrum became progressively more severe. He had chills and fever to 105 degrees, and his blood pressure rose to 200/100. Following the second administration of the fibrinolytic agent there was some improvement. On August 16 bishydroxycoumarin was started, and the prothrombin time became elevated, ranging from 17.5 to 50 per cent.

He continued to have pain and paresthesias of the feet, particularly of the left foot and calf. On September 1 he complained of frontal headache, and began to have episodes of vomiting so severe that he required parenteral fluids. His blood pressure was 230/110 with a full bounding pulse. The peripheral pulses of the lower extremities were palpable, and a grade II systolic murmur, which had previously

Edited by Jesse D. Rising, M.D. and Mahlon Delp, M.D. from recordings of the conference participated in by the departments of medicine, pediatrics, surgery, radiology, and pathology of the University of Kansas Medical Center as well as by the third and fourth year classes of students.

disappeared, was again noted. By September 6 he was critically ill, incoherent, confused, and lethargic. Rales were heard in both lung fields. He died on September 10, 1957.

Dr. Mahlon Delp (moderator): Are there any questions?

Orlyn Engelstad (student):* Were any hemoglobin values obtained other than the one on admission?

Dr. Wu-Hai Tu (resident in medicine): The hemoglobin ranged from 9.0 to 13.6 gm.

Don Ginardi (student): What were the blood urea nitrogen levels?

Dr. Tu: The blood urea nitrogen was from 13 mg. per cent to 103 mg. per cent.

Ashford Galbreath (student): What was his urinary output?

Dr. Delp: On September 5 his output was 1200 ml.; on September 6, 750 ml.; and on September 7, 800 ml.

Donald Hayen (student): Was abdominal distention associated with the pain?

Dr. Tu: There is no mention of any abdominal distention.

Albert Duncan (student): Did he have any chest pain?

Dr. Tu: No, he did not.

Orville Boicourt (student): Did he have any retinopathy late in his course?

Dr. Tu: No, he did not.

Mr. Ginardi: Did he have a previous history of kidney infection?

Dr. Delp: No, he apparently had been perfectly well until the onset of his illness.

Kenneth Kihle (student): Was there any lymph node enlargement?

Dr. Sloan Wilson (hematologist): He had no enlarged lymph nodes.

Mr. Boicourt: Did he ever have purpura?

Dr. Wilson: No, he did not.

Mr. Engelstad: What were the potassium values?

Dr. Delp: They were extremely low.

Mr. Kihle: Will you describe his terminal event?

Dr. Delp: Dr. Larsen, will you tell us about that, please?

Dr. William E. Larson (hematologist): Terminally, the patient had congestive failure and acute pulmonary edema.

Mr. Duncan: Were there signs of embolization?

Dr. Delp: There were no splinter hemorrhages.

Mr. Hayen: Did the onset of his leg pain occur suddenly?

Dr. Delp: The pain gradually progressed from the time he became ill.

Mr. Ginardi: Were any blood cultures done?

Dr. Delp: No.

Mr. Boicourt: Was he given any antibiotics?

Dr. Delp: Yes, he received antibiotics and a number of other medications. If there are no more questions we will have the electrocardiograms.

ELECTROCARDIOGRAMS

Mr. Boicourt: The first electrocardiogram taken on September 7 shows a normal sinus rate of approximately 120. The P-R, QRS and QT intervals are normal. There is non-specific T wave flattening in leads I and V_6 and minimal S-T segment elevation in lead V_2. There are several venticular prematurities in leads I, II, III, V_4R and V_2. I interpret this as a sinus tachycardia with ventricular premature contractions.

A tracing on September 8 shows the inversion of T waves in lead aV1. There is continued S-T segment elevation in lead V_2 and V_3 and a suggestion of a biphasic T wave in both leads.

A tracing taken on the day of death shows a low amplitude R wave with S-T segment elevation and inversion of the T wave in leads V_2, V_3 and V_4 and a definite decrease in the R wave in leads V_4, V_5 and V_6 *(Figure 1)*. I interpret this tracing as suggestive of myocardial infarction.

Dr. Delp: From the appearance of these tracings, Dr. Larson, do you believe that the patient had a myocardial infarction?

Dr. Albert Jackson (internist): No, I do not.

X-RAYS

Dr. Delp: May we have the x-rays now, please?

Dr. Galbreath: An intravenous pyelogram taken

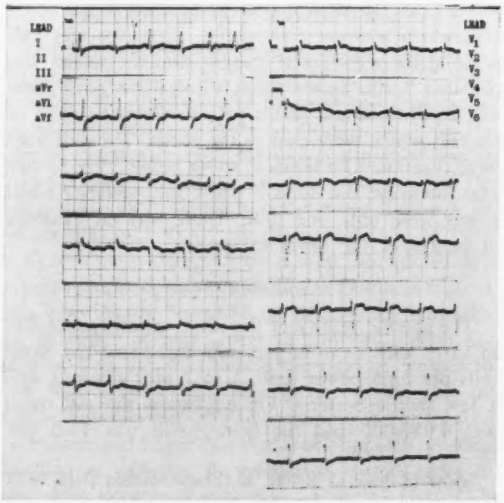

Figure 1. Electrocardiogram taken on the day of death, September 10.

* Although a student at the time of this conference in November, 1958, he, like the others referred to as students, received the M.D. degree in June, 1959.

on September 4 *(Figure 2)* shows some collection of radio-opaque material in the right kidney. The left kidney is obscured by overlying bowel, gas and feces. Because there is no flat plate of the abdomen it is difficult to determine whether this is calculus. There is some dilatation of the calyces, and the spleen is enlarged.

A 4-minute film shows essentially the same findings, and no bony abnormalities are seen. There is no collection of radio-opaque material in the ureters, and there is no outline of the kidney on the left.

An upper gastrointestinal series taken on the day of admission is normal, and there is no evidence of a mass. There is some indention by the enlarged spleen, but I interpret this as a normal film.

A chest film on August 20 shows no bony abnormalities. The posterior diaphragmatic areas and the lung fields are clear. No bony abnormalities are seen except for a mild scoliosis of the thoracic vertebra. The heart is normal, and there is no hilar adenopathy. The angles of the diaphragm are normal and clear, and I interpret this as a normal chest film.

Dr. Delp: Thank you. May we have your comments, Dr. Germann?

Dr. Donald R. Germann (radiologist): A number of other films showed that this was not a staghorn calculus. The chest and upper gastrointestinal series were normal. The intravenous pyelogram was of interest because of the marked delay in kidney function. The left side was poorly outlined and showed some hydronephrosis. The most significant finding of the x-ray was the poor kidney function on the left.

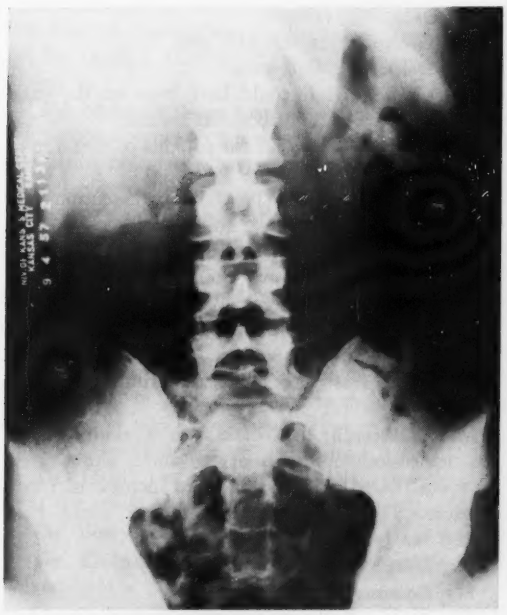

Figure 2. Intravenous pyelogram taken on September 4.

Dr. Delp: Thank you. May we have your differential diagnosis now, Mr. Kihle?

Differential Diagnosis

Mr. Kihle: This 38-year-old man was admitted here complaining of pain and weakness in both legs for about two weeks' duration. He had no definite symptoms until his hospitalization elsewhere when he developed chills and fever. Physical findings showed generalized pallor, a palpable liver and spleen, a grade II systolic murmur, diminished pedal pulses, cyanosis, and coldness of the feet. There was marked leukocytosis, predominantly of immature mononuclear blast cells, and a low platelet count. The hemoglobin was 13.7 gm.

Eleven days after admission all of the pulses were absent in the lower extremities. On the following day he developed buttock and testicular pain associated with nausea and vomiting and a rise in blood pressure. His condition became progressively worse, and he died on the 38th hospital day.

I shall base my differential diagnosis on marked leukocytosis, hypertension, immature cells in the peripheral blood, thrombocytopenia, and hepatosplenomegaly. Leukemoid reaction is suggestive of leukemia and occurs under a variety of circumstances including infections, intoxications, malignancies and following severe hemorrhage. The clinical features which distinguish leukemoid reactions are marked immaturity of the cells, lack of evidence of hemopoietic disturbances such as immature circulating red cells, platelet abnormalities, and sternal tenderness. I conclude that this patient did not have leukemoid reaction.

The lymphomas, which include the lawless proliferation of lymphocytic cells, can be ruled out because there was no generalized lymphadenopathy or x-ray fiindings to support that diagnosis.

On the basis of its clinical course leukemia may be classified as acute, subacute or chronic. Early a chronic leukemia with relatively acute symptoms may develop with acute exacerbations, but because the white count was from 60,000 to 120,000 with 90 per cent immature mononuclear blast cells, and because the clinical course was seven weeks duration, my diagnosis is acute leukemia. Weakness and pain in both legs could have been due to subperiosteal and periosteal infiltration, but may have been the result of arterial insufficiency with paresthesias, progressive cyanosis and rapidly diminishing peripheral pulses. Because the pain was migratory one would suspect a process of partial occlusion in the arteries of the legs ascending up into the femoral and iliac areas and into the aorta.

Arterial Embolism

I will first consider embolization as a possible cause of the pathological process. There is a marked hemorrhagic tendency in most cases of acute leukemia. Numerous cases have been reported of hemorrhage and leukocytic infiltration of the heart muscle with thrombus formation in the left ventricle, but one would expect to find more evidence of embolization in other parts of the body.

Non-bacterial thrombotic endocarditis characterized by verrucous endocarditis is seen in a variety of infections and in acute and chronic wasting diseases such as leukemia. The essential characteristic of that disease is the presence of a non-specific valvular vegetation along the closing line of the cusps. Microscopically there are agglutinated blood platelet thrombi. The fact that our patient had a changing aortic murmur would, however, make one suspicious of that diagnosis. Leukemic involvement of the periaortic nodes could theoretically lead to compression of the aorta, but that is unlikely.

Mucormycosis is occasionally seen as a complication of leukemia and is unique among the microorganisms in that there is a greater tendency for involvement of the blood vessels by penetration of the muscular walls. It simulates arteritis with thrombus formation and later involves the veins and lymphatics. It has been reported that there is an increase in patients with leukemia, diabetes and tuberculosis, and there may be involvement of the coronary artery with thrombosis in the disseminated forms. No reports were found in the literature, however, of involvement of the aorta.

In acute leukemia the walls of the large arteries and aorta may have leukemia infiltration which can serve as a nidus for the formation of a thrombus which may progress to occlusion of the larger vessels.

A review of the literature supplied only one case of large artery thrombosis in acute leukemia, but capillary and venous thromboses are seen occasionally. The patient's history suggests arterial insufficiency. I believe that small artery thrombosis developed with proximal extension into the larger vessels. Because gangrene of the extremities did not develop there may have been only partial occlusion of the arterial supply. The thrombotic process extended proximally into the aorta causing gluteal and testicular pain. There was complete absence of femoral, dorsalis pedis and posterior tibial pulses, and the feet were cold to the touch. At that time the thrombotic process was obliterating the iliac vessels and extending into the aorta. On the thirteenth hospital day the patient's blood pressure was 180/100, and he had nausea, vomiting, and severe pain in the lower abdomen and testicles. The occluding process then involved the renal and spermatic arteries. Chills and fever followed the administration of a fibrinolytic agent, but that may have been a side reaction of the fibrinolysis. After a second administration of the fibrinolytic agent the patient had some relief of his symptoms; the peripheral pulses became palpable, and there was recanalization of the thrombus.

Anticoagulant therapy was begun, but his condition again became worse. His blood pressure rose to 230/110 which can be explained on the basis of renal artery thrombosis in which there is usually a rapid rise in blood pressure. Terminally, he vomited considerably and was confused and lethargic, but it is questionable whether those symptoms were the result of a hypertensive encephalopathy which is often seen in a rapidly rising blood pressure of renal origin. There was temporary improvement of the rales which had developed in both lung fields, but they recurred terminally and probably were the result of left ventricular failure.

In summary, I believe our patient had an acute leukemia with an ascending arterial thrombosis involving the aorta and renal arteries and resulting in hypertension and death.

Clinical Discussion

Dr. Delp: Thank you. What was the etiology and the pathogenesis for his congestive heart failure, Mr. Hayen?

Mr. Hayen: Leukemic infiltration of the myocardium.

Dr. Delp: Mr. Ginardi?

Mr. Ginardi: I agree with that.

Dr. Delp: Mr. Galbreath?

Mr. Galbreath: It could have been on the basis of hypertension or a myocardial infarct.

Dr. Delp: Is it unusual for patients of that age to go into congestive failure?

Mr. Galbreath: The onset of hypertension was rather sudden, but it is not impossible.

Dr. Delp: What is your opinion, Mr. Duncan?

Mr. Duncan: Coronary arteriosclerotic disease is not uncommon at that age.

Dr. Delp: Since the patient was not in congestive failure on the day of admission, could there have been another reason for his heart failure, Mr. Galbreath?

Mr. Galbreath: His heart was working against the tremendous occlusion of the aorta, and a great load was placed on it by the rapid increase of blood pressure. Together, these two factors could have caused his failure.

Dr. Delp: Mr. Boicourt?

Mr. Boicourt: I agree with that.

Dr. Delp: Will you review the suggestions that have been made as to the cause of his congestive failure, Mr. Kihle?

Mr. Kihle: Leukemic infiltration of the myocardium, the partial aortic occulsion, and the acute hypertension.

Dr. Delp: Mr. Etzenhouser?

Russell Etzenhouser (student): There may have been pericarditis.

Dr. Delp: Mr. Engelstad, what is the significance of the low sodium and chloride values?

Mr. Engelstad: The patient could have had a hypervolemia.

Dr. Delp: What would cause him to have a hypervolemia?

Mr. Engelstad: He may have been sensitive to anti-diuretic hormones thus producing a retention of water.

Dr. Delp: Mr. Ginardi?

Mr. Ginardi: I agree with that, but there was also the possibility of overhydration.

Dr. Delp: What would cause overhydration?

Mr. Ginardi: The administration of intravenous fluids.

Dr. Delp: Mr. Hayen, what is your opinion?

Mr. Hayen: The patient had some kidney insufficiency and retention of water later in his course.

Dr. Delp: Mr. Engelstad, what is the usual renal output when there is a low sodium and chloride?

Mr. Engelstad: About 500 ml.

Dr. Delp: Mr. Ginardi?

Mr. Ginardi: We have to depend on the mechanism we are postulating. Because of the anti-diuretic hormone he would probably have less of a diuresis and a low output, but he was receiving large amounts of fluid and he still could have had a good output.

Dr. Delp: May we have your comments, Dr. Berry?

Dr. Maxwell Berry (internist): In acute leukemia thrombosis occurs within the lumen of the aorta, and does not necessarily have to propagate from below. I believe the patient's problem was intraluminal thrombosis of the aorta with progression upward to involve the left kidney. The artery to the kidney was partially or completely occluded. The terminal part of his illness was a reaction to the load of the acute hypertension, together with numerous other factors. I can not help but believe that he had an acute hypertension and acute congestive heart failure. There was, of course, some interference with his oxygenation which was, among other things, probably the result of loss of hemoglobin.

Dr. Delp: Do you believe that his hypertension was the result of the blocked aorta?

Dr. Berry: No, I do not.

Dr. Delp: May we have your comments, Dr. Manning?

Dr. Robert Manning (internist): The patient's terminal event could also be theorized on the basis of liver failure. Enlargement of the liver with probable leukemic infiltration, a high white count, and ascites in the abdomen usually are associated with low sodium and chloride and low renal output. These factors could also contribute to his congestive failure and fluid overload.

Dr. Delp: Dr. Jackson, have you seen many patients with congestive heart failure as a result of leukemic infiltration of the myocardium?

Dr. Jackson: No, I have not.

Dr. Delp: Do you believe that that is what happened here?

Dr. Jackson: No, I believe the patient's hypertension was due to an increase in peripheral resistance which, in turn, was due to the occlusion of the renal arteries and resulted in failure. The left ventricular failure could also explain the low sodium and chloride. I believe that he did have an infiltration of the pericardium.

Dr. Delp: Did the hypertension develop too suddenly to be the result of the non-functioning kidney?

Dr. Jackson: No, I do not believe so.

Dr. Delp: Can we assume that the patient had a properly functioning kidney before the onset of his illness?

Dr. Jackson: It is possible.

Dr. Delp: The students claim that the patient had leukemia and a blocked aorta. May we have your comments regarding the aorta, Dr. Wilson?

Dr. Wilson: Arteries can be involved in various ways. One case in the literature reports a patient with complete rupture of the aorta from infiltration of the vessel wall with leukemic cells. Other cases have been reported in which the actual infiltration in the vessel wall started a thrombotic type of episode; however, little is known about the study of hypercoagulation of the blood. One theory is that because there are so many of these cells more tissue extract is released causing hypercoagulation of the blood with thrombus formation. On occasion one may see a patient with hemorrhage which requires posterior nasal packs, while at the same time there is a thrombotic episode in another part of his body. We are caught between two extremes, either to use an anticoagulant or to attempt to lyse a thrombus that has already been formed.

Dr. Delp: Thank you. Dr. Higginson, may we have your report now, please?

Pathological Report

Dr. John Higginson (pathologist): The patient was well nourished and showed no significant lesion on external examination apart from numerous ecchymoses which were most marked around needle puncture wounds.

On naked eye examination the bone marrow had a rather creamy, purulent appearance. On microscopy the marrow was almost completely replaced by leuke-

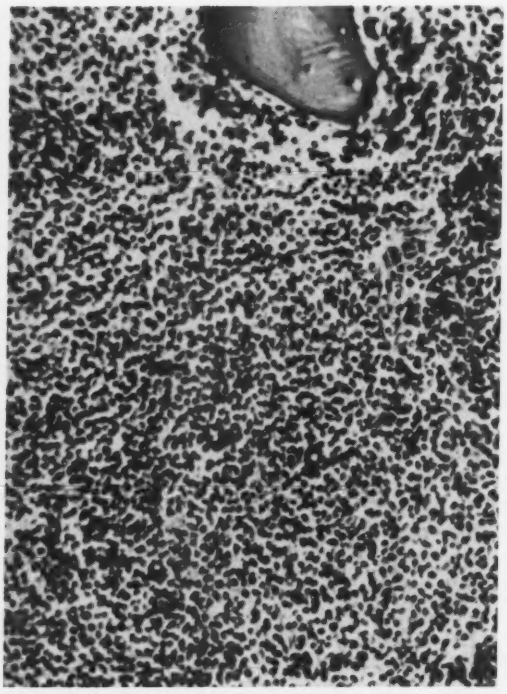

Figure 3. Section of acute leukemic bone marrow showing replacement by numerous primitive blast cells. H & E x 155.

mic cells with large nuclei containing irregularly dispersed chromatin and surrounded by relatively scanty cytoplasms *(Figure 3)*. The spleen was a dark reddish-brown in color and enlarged, weighing 840 gm. A cone-shaped white infarct (3 cm. in width) with hemorrhagic margin was present on the parietal surface. In addition to leukemic infiltration, foci of extra-medullary hemopoiesis were also present.

Scattered small infiltrates by leukemic cells were also found in the capsule and sinusoids of the liver, in the wall of the intestine, the kidneys, bladder, testes, adrenals, lymph nodes, and skin.

The most striking features were in relation to the aorta and kidneys. The abdominal aorta contained a large thrombus which extended from above the renal arteries into both common iliac arteries. It also partly filled the left renal artery. The greater part of the thrombus appeared recent, being brown, friable, and loosely adherent to the wall. The right kidney was somewhat larger and paler than the left; the right kidney weighed 240 gm., the left kidney, 190 gm. The latter, however, showed areas of irregular pallor of the cortex suggesting cortical infarction.

On sectioning the aorta, a considerable degree of atherosclerosis was seen covered by an overlying thrombus. While the latter showed early organization, the greater part appeared relatively recent *(Figure 4)*.

The left kidney showed areas of coagulative necrosis involving the greater part of the cortex and the medulla. In the remainder of the organ many of the interlobular arteries had thickened edematous walls which sometimes were occluded by fibroblastic thickened intima and sometimes by thrombus. In the relatively intact areas the glomeruli and afferent arterioles were normal. In the right kidney there were numerous foci of fibrinoid necrosis in the afferent arterioles and in the glomeruli *(Figure 5)*. Such lesions are observed in acute hypertension, and are believed to be a reaction to rapid rises in blood pressure.[1]

The lungs were much heavier than normal and weighed 3,080 gm. All lobes were dark red and of a firm, meaty consistency. The cut surface was dry, and fluid could not be readily expressed. On microscopy, the alveoli were filled with varying amounts of edema fluid, fibrin, and red cells; in some areas, leukemic cells were prominent *(Figure 6)*. The latter were also seen in the capillaries throughout the lungs.

Of the remaining organs the heart was somewhat increased in weight (510 gm.). The liver weighed

Figure 4. Section through wall of abdominal aorta showing unorganized thrombus, atheromatous thickening of the intima and vascularization and inflammation of the media. H & E x 44.

2,820 gm. and showed accentuation of the normal lobular pattern. In addition, many small intrahepatic veins were occluded by yellowish-white thrombi showing varying degrees of organization. The lymph glands were not unduly enlarged.

In summary, the patient had an acute leukemia, the exact cell type of which is uncertain, although the cells most suggested a Shilling type of monocytic leukemia. Thrombosis developed on a moderately atherosclerotic aorta, and this resulted in ischemia of the left kidney due to obstruction of the renal artery. The resultant Goldblatt mechanism led to an acute rise in blood pressure, as observed clinically, and to the necrotizing arteriolitis seen in the unprotected right kidney.[2] Progressive renal failure finally ensued, and death resulted from a terminal hemorrhagic bronchopneumonia.

The changes in the other organs are incidental to the leukemia, but the thrombus of the aorta requires further comment. The presence of the thrombosis in association with a hemorrhagic diathesis is difficult to explain. It is possible that it may be related to destruction of leukemic cells of the monocytic type with resultant release of thromboplastin.[3] However, such a mechanism is rare. On the other hand, it is not uncommon to see intra-aortic thrombi superimposed on moderate atherosclerosis in elderly people for which no other specific cause can be found.

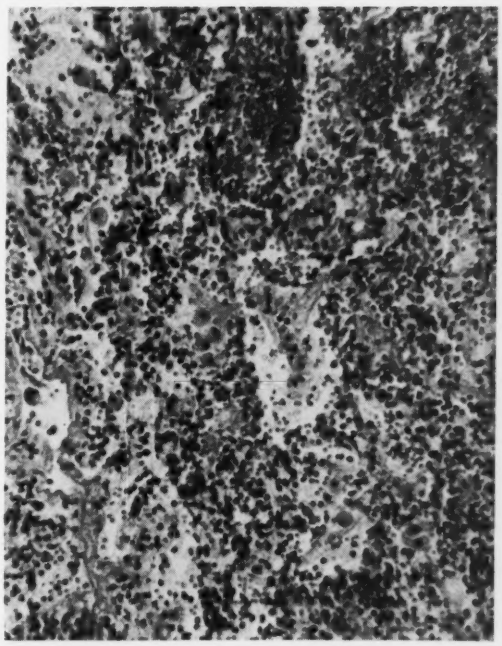

Figure 6. Section of the lung showing infiltration of red cells, leukemic cells, also fibrin into the alveoli. H & E x 155.

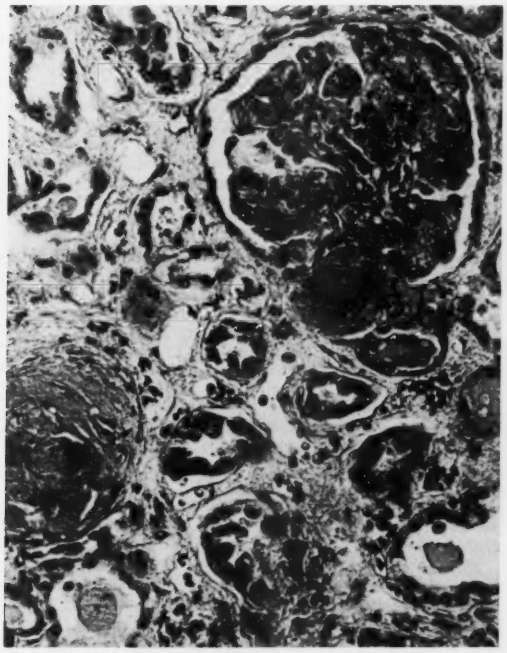

Figure 5. High power view of right kidney showing an almost completely sclerosed glomerulus. A second glomerulus shows fibrinoid necrosis of the afferent arteriole. H & E x 300.

Dr. Delp: How long do you believe the thrombus had been in the aorta?

Dr. Higginson: It appeared to me that it had been in the aorta for the last two or three weeks. However, it is possible that there may have been an earlier thrombus which broke off, and there may have been a second superimposed thrombus since there was some difference in the degree of organization.

Dr. Delp: How far did the thrombus extend?

Dr. Higginson: It extended into the common iliac arteries and about 11 cm. above the renal artery. Unfortunately, it was not possible to open the leg arteries.

Dr. Delp: Are there any other questions?

Mr. Engelstad: Can you tell us about the adrenals?

Dr. Higginson: There was no abnormality of the adrenals except for some leukemic infiltration of the zone reticularis and fasciculata.

Summary

Dr. Delp: As a complication of acute leukemia a whole series of progressive signs and symptoms (*i.e.* pain in the legs, perineum and back, cyanosis and diminishing pulse in the lower extremities) gave

the clinicians ample opportunity to predict the uncommon situation of thrombotic obstruction of the aorta from the iliacs to some point above the origin of the renal arteries. The clearly documented, marked increase in the blood pressure was adequate evidence of nature's spontaneous production of a Goldblatt kidney model.

Pathological Anatomical Diagnosis

Acute leukemia involving the marrow, liver, spleen, and lymph nodes with focal infiltration of the heart, kidneys, adrenals, skin, stomach, pancreas, and testes.

Unorganized thrombus occluding the abdominal aorta, extending from 2 cm. of both common iliac arteries to 1 cm. above the renal arteries with extension into the left renal artery, 1 cm.; with recent thrombus extending to 11 cm. above the renal arteries.

Organizing infarction of the peripheral cortex of the left kidney.

Acute necrotizing arteriolitis of the right kidney.

Hypertrophy and dilatation of the heart.

Acute hemorrhagic bronchopneumonia.

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Primary Aldosteronism

(Continued from page 171)

data presented here confirms these reports of the effectiveness of spirolactones in antagonizing the effect of aldosterone excess. A definite negative sodium balance was induced. Potassium balance was little affected although urinary excretion of potassium was decreased while fecal potassium increased. The positive potassium balance throughout is probably related to the patient's total body potassium deficit plus the fact that she was receiving a low sodium diet.

Supported in part by Research Grant A-1709 (C2), National Institute of Arthritis and Metabolism.

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Committee
REPORTS

Defective Hearing in Children

Part V—Evaluation of Clinical Data

C. W. ARMSTRONG, M.D., *Salina*, Editor

THE EVALUATION OF CLINICAL data in defective hearing depends upon the interest and ingenuity of the individual physician. The majority of diseases which produces a decrease in hearing, can be managed in a more intelligent manner if an audiogram of some type is available. This allows the physician to have an objective measurement not only of the hearing loss at the onset but also a means by which he can measure the improvement in hearing as therapy progresses. The small otometer is of value for this purpose.

Most Common Defect

The most commonly observed form of defective hearing is due to eustachian tube blockage which is frequently referred to as eustachian salpingitis or tubotympanitis. This condition usually occurs in conjunction with upper respiratory disease, however, it may occur with such negative findings as an apparently normal tympanic membrane, normal nasal passages and no enlargement or infection of the tonsils and adenoids. When it does occur without other disease being apparent, the audiogram does not always follow a fixed pattern. In general the condition tends to produce a hearing loss for the lower frequencies only. This is the result of closure of the eustachian tube and its attendant hearing loss due to a lack of equalization of the air pressure on the two sides of the tympanic membrane.

A series of six articles on Defective Hearing in Children is being printed in the *Journal*. These articles were prepared by C. W. Armstrong, M.D., Salina, Kansas, for the Committee on Conservation of Hearing and Speech. The committee members are V. R. Moorman, chairman, C. W. Armstrong, J. A. Budetti, R. A. Draemel, E. L. Gann, C. L. Gray, W. P. McKnight, E. E. Miller, Ruth Montgomery-Short, W. D. Pitman, R. R. Preston, G. O. Proud, R. E. Riederer, and M. J. Ryan.

The title of the coming article will be Conclusions.

In otitis media, the audiogram tends to assume a more nearly flat appearance. The loss is about the same for all frequencies. Otitis media, especially the acute and purulent type, are easily diagnosed by clinical means, but their progress is more satisfactorily followed when audiometry is added to the other methods of evaluation.

This is the fifth article in a series of six prepared by the Kansas Medical Society Committee on Conservation of Hearing and Speech. They are edited by Dr. C. W. Armstrong, Salina. The final article will appear in the April issue of the JOURNAL.

Hearing losses are observed by audiometry in conjunction with other upper respiratory disease such as the acute phase of tonsil and adenoid disease even when there is no gross obvious hearing loss. Here, there is no fixed pattern but there is satisfaction to be gained in measuring an otherwise uncertain loss of hearing.

Chronic middle ear disease may have a fairly good prognosis if the hearing defect is not severe and the mastoid x-ray is negative.

Has a Flat Audiometric Curve

Serous otitis media is a common condition and may be unilateral or bilateral. There is a moderate to severe defect of hearing with a fairly flat audiometric curve. This condition is recognized by the variable position of the tympanic membrane, the lack of inflammation, and the presence of clear to brownish fluid in the middle ear. Occasionally, bubbles or a fluid line may be present. If bubbles are present and there is no active upper respiratory infection, Valsalva inflation is often a sufficient form of treatment. Repeated myringotomies with aspiration of the middle ear fluid may be necessary in the ear with persistent fluid.

Defective hearing due to the presence of cerumen and debris in the external ear is easily diagnosed and usually can be improved immediately by adequate removal of the offending material.

The person with recurring upper respiratory infections or a "perennial cold" should be viewed in relationship to his environment. For example, the parent who holds two jobs to provide his family with the necessities of life may have a low vitality and be the carrier of a low grade infection. He can be the host from whom the child gets his recurring infection which caused the child's anemia and debility. The cause of such perennial colds and debilities must be diligently sought and if possible corrected.

Refer to Otologist When Present

There are certain conditions which probably should be referred to an otologist. Among these are aural polyps and granulation tissue which is found while the ear is being cleaned. The polyps usually protrude through a tympanic perforation and are frequently attached to vital structures such as the dura mater, the facial nerve, or to a fistula of one of the semicircular canals. Another such condition is cholesteatoma in which cakes of epithelial debris are found to be coming through a perforation of the drum membrane. This is due to the presence of squamous epithelium behind the drum membrane and surgical treatment is frequently necessary.

The diagnosis of hearing defects is not merely a matter of audiometry but is an evaluation of all the clinical data. The audiogram establishes the degree of the hearing defect, and repeated audiograms are a distinct aid in following the progress of the patient under treatment.

(To be continued in the next issue of the JOURNAL.)

710 United Building
Salina, Kansas

Job Heart Attacks

Only one of five heart attacks occurs on the job, according to the current issue of *Patterns of Disease,* prepared by Parke, Davis & Company for the medical profession. Moreover, an increasing number of heart disease victims can and do return to work, the publication reveals.

Evidence for these statements is based on a survey of 112 companies in Minnesota. The survey showed that about two-thirds of patients surviving attacks return to their former place of employment, almost one-half of these returning to their former jobs.

Rehabilitation, vocational guidance, and selective placement of cardiac patients make it possible for an increased number of persons to resume work.

However, many companies remain reluctant to hire cardiac victims. The Minnesota survey showed, for instance, that nearly 60 per cent of companies seldom or never hire persons with known heart disease, and about 3 per cent of them require cardiac employees to seek work elsewhere.

A large factor in reluctance of employers to hire cardiac patients is consideration of Workmen's Compensation or group insurance and sick-leave liability claims.

Maternal Mortality

A 20 year old primigravida died following delivery of a normal seven pound, ten ounce infant. Death was attributed to intracranial hemorrhage due to eclampsia. Findings were supported by autopsy.

The patient's medical history revealed no points of significance and family history was also non-contributory. Her prenatal care was initiated early in pregnancy and was consistent. Routine laboratory work-up was performed.

The first indication of trouble occurred during the last month of pregnancy, some 17 days prior to delivery, when a trace of albumin was noted on routine urinalysis. One week later this was two plus, but there were no other abnormalities. This finding was repeated at the next visit which was two days prior to hospital admission. A gain of 19 pounds in the last six weeks was noted, the total for the full pregnancy being 36 pounds. Blood pressure during the last weeks of pregnancy varied from 124/84 to 148/110, the latter being at the visit two days before admission. Mild edema of the lower legs was noted in the latter weeks. Otherwise, there were no significant symptoms or findings during the prenatal period.

The indications of toxemia prompted the physician to advise elimination of salt from the diet, bed rest, and sedation. She was instructed to return to the office for a recheck the next day, but instead the patient went into labor spontaneously and was admitted to the hospital that day.

Upon hospital admission, a blood pressure of 168/110 and two plus edema was noted. Urinalysis disclosed four plus albuminuria. Labor progressed steadily but the patient was thought to be in a preconvulsive state because of persistent drowsiness. Forty-four minutes prior to delivery a generalized convulsion occurred. The following medications and procedures were instituted: Continuous oxygen by pressure mask, and later, tent; sodium amytal and pentothal to control impending convulsions; magnesium sulfate 50 per cent, two cc. every four hours; 10-20 per cent glucose in water in water in small amounts; continuous Fowler's position; Unitensin® during delivery; and then continuously intravenously; spinal anesthesia for delivery; prophylactic antibiotic. Consultation was obtained with another obstetrician, an internist, and an ophthalmalogist. Delivery was accomplished by low forceps with an episiotomy, and the placenta was delivered with mild fundal pressure. Following delivery, the patient's condition went steadily downhill, and she died seven hours after delivery.

Autopsy findings included "cerebral hemorrhage into the ventricular system (left lateral ventricle), massive, with brain destruction," bilateral congestion and edema of the lungs, and moderate congestion of the liver. The case was reviewed by the hospital staff.

Committee Opinion

The committee felt that the cardinal signs of preconvulsive toxemia (albuminuria, excessive weight gain with edema, elevated blood pressure) were recognized by the attending physician, but not actively treated soon enough. The outcome of the case might have been altered had earlier hospitalization been advised. Hospital management was considered adequate.

Classification

Maternal death, direct obstetric, avoidable.

One of a series of case reports prepared by the Committee on Maternal Welfare to illustrate the type of study made in each instance of maternal death in Kansas.

Editorial Comment

This JOURNAL welcomes to its staff Dr. Jesse D. Rising of the University of Kansas Medical Center. Doctor Rising is now filling the position formerly held by Dr. Vernon E. Wilson—that of Associate Editor representing the Medical Center. He has previously contributed of his talents in the editing of some of the clinical pathological conferences.

This issue of the JOURNAL is the 14th Annual University of Kansas Issue, and the work of assembling and editing the material has been done by Doctor Rising. We are grateful to him and to the numerous contributors for the excellent material here provided. The University Issue has become recognized as an outstanding number each year and we appreciate the privilege of continuing it from year to year.

Orville R. Clark, M.D.—Editor

From the Stacks

Medical Books and Libraries in Kansas

The first issue of the new *Index Medicus* (January 1960) has now reached the medical libraries of Kansas and, lest a highly significant event pass unnoticed, this first column of a series on medical literature and libraries in Kansas is devoted to it and to a proposal for better library service to Kansas physicians.

For nearly 20 years there have been two major indexes to medical periodicals, the A.M.A.'s *Quarterly Cumulative Index Medicus* and the National Library of Medicine's *Current List of Medical Literature.* Many people have relied heavily on the *Quarterly Cumulative* in preference to the *Current List* in their efforts to keep up with the literature because it was simpler to use. The *Current List* won its place by living up to its name in being current as well as comprehensive. In place of both these we now have the *Index Medicus,* published monthly by the National Library of Medicine and available for 20 dollars a year through the Superintendent of Documents, Government Printing Office, Washington 25, D. C. The American Medical Association, as its share of responsibility, will publish annual cumulations of the index under the title *Cumulated Index Medicus.* The price of this has not yet been announced.

Index Medicus

The *Index Medicus,* which will gradually be enlarged in its coverage, is the most extensive indexing service of the literature of a specialized subject and it affords to Kansas physicians, as to all others, the key to a very large part of the world literature of medicine. The National Library of Medicine which published it is at the top of a pyramid of library service which has at its base thousands of small local libraries in hospitals and medical societies. The plan of service is based on the assumption that a physician in need of literature will first exhaust the local facilities, whatever they may be, then the statewide services such as are offered by the Stormont Medical Library in Topeka and the Clendening Medical Library at the University of Kansas Medical Center, and finally the National Library itself which, however, will lend directly only to other libraries.

The lack of local facilities is often the weak link in the chain of library service. It would seem reasonable to suggest that every hospital and medical society in Kansas, even if it supports no library of its own, should acquire as a top-priority purchase the *Index Medicus* or its cumulation. By collecting references from its pages and requesting loans from the Stormont or Clendening Libraries of specific articles of his own choosing, rather than by sending blanket requests for material on vaguely defined subjects, the Kansas doctor can gain quick access to perhaps half of the more than 100,000 journal articles a year which will be covered by the *Index Medicus.*

A Suggestion

In Kansas no more than eight medical libraries exist which meet the standards of the Medical Library Association. There are, however, probably two hundred established public libraries which would be willing to service the *Index Medicus* if a subscription were placed there by the local medical community. In most cases the public libraries could also make loan requests to other libraries on behalf of their medical patrons, and handle the mailing which can be done at a preferential rate between non-profit institutional libraries.—G. S. T. Cavanagh, *Clendening Medical Library, University of Kansas Medical Center.*

Executive Stress

The stresses of executive life do not take the high toll expected, according to the current issue of *Patterns of Disease,* prepared by Parke, Davis & Company for the medical profession.

Contrary to popular belief, executives do not have a higher incidence of heart conditions or tension disorders than other employees with less responsibility.

In fact, one large scale study of close to 1,400 employees revealed, surprisingly, a slightly lower incidence of such conditions as hypertension, arteriosclerosis and myocardial infarction among executives than nonexecutives. In another study analyzing the prevalence of some 16 medical conditions among employees (including anxiety states, peptic ulcer, and gastrointestinal diseases), only two conditions ranked significantly higher among executives. They were arthritis and rheumatism and "back" cases (both twice as high). On the other hand, hernias occurred almost three times as frequently among nonexecutives.

Possibly executives are healthier than other workers to start with, or have means of releasing tensions, or take better care of themselves than other workers.

The President's Message

DEAR DOCTOR:

Many leaders of American Medicine view the coming months of the second session of the 86th Congress as the most critical ones ever confronting our profession, even including the days of the all out push for compulsory federal health insurance during the Truman administration.

We have arrived at a situation where it is estimated that 44 per cent of the nation's medical bill for the last year was paid by a local, state or federal agency. In California eleven per cent of its revenue, in 1958, was spent on state financed medical care for over one half million of its citizens. A very large percentage of our entire population is eligible for some sort of federal health care.

Is the private practice of medicine, the free enterprise and competitive system, which has resulted in such high standards of health care for the American public to be swallowed piecemeal until it no longer can exist without government subsidization? Is this the strategy with which our opponents seek to gain control over our profession? If so, the plan seems to be destined for success, unless blocked by effective counter offensives.

All out attempts have been made by the A.M.A., your state society, and most local components to warn the profession of the seriousness of the situation. Yet many of our members still are not aware of the provisions and pitfalls of the Forand type of legislation which may come before Congress at any time. Despite the protestations of the sponsors to the contrary, this proposed act is socialization and must be recognized as such. Business leaders know this fact and are backing the medical profession in its fight, because after socialization of medicine, governmental control of banking, manufacturing, the practice of law, the railroads and many other businesses is but a simple step away.

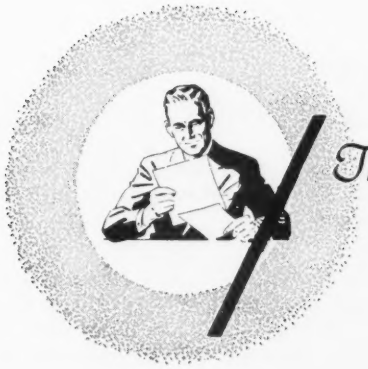
Your county, state and national medical societies are the logical agencies through which the physician can plan an effective part in this fight. Over the past few years there has been a decline of interest in these organizations because of the shift of emphasis on scientific postgraduate education from the medical society to speciality groups, general practice groups, refresher courses, etc. This has perhaps been beneficial from the viewpoint of the dissemination of scientific information but has deprived the medical society of many excellent leaders and of much interest in the political and economic aspects of medical practice with which medical societies must concern themselves.

The 1960 meeting of the Kansas Medical Society will be in Hutchinson, May 2, 3, and 4, as has been announced in the JOURNAL. Now is the time to make your plans to attend. It is imperative this year, perhaps as never before, that officers and delegates of county societies attend the business sessions of the House of Delegates in full numbers. The Reno County Society has arranged an interesting program and fine entertainment. Your hosts will be happy to see each one. You will be better informed on medical society matters for having attended and will be royally entertained. Bring your wife and we'll see you in Hutchinson.

Fraternally,

Glenn R Peters M.D

President



The Business Side of Medicine

A Comparison of Permanent and Term Life Insurance

FLOYD F. WEHRENBERG, ***Kansas City, Missouri***

Many articles have been written and much discussion carried on concerning the most economical form of insurance to carry. For some years we have recommended term insurance for temporary short term needs and ordinary or whole life for permanent needs. Our reason for this recommendation is that if you live to retirement age, ordinary or whole life insurance will have the lowest net cost. In comparing cost it is necessary to assume survival to retirement age. Obviously, if death occurs shortly after taking out insurance, term insurance would have been least expensive but there is no way of knowing this in advance. Our primary goal is to provide the necessary insurance protection in case of death in a form that will return the largest portion of your premium in case you live.

Comparison of Term and Ordinary

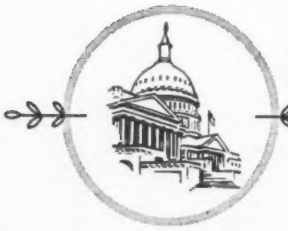
In order to compare the net costs of term insurance and ordinary or whole life, we have prepared the following illustration. Let us assume that the policyholder takes out a $10,000 policy at age 35 and it is carried to age 65. We are also considering a 3 per cent return on the premium difference between the two types of contracts on the assumption that the premium difference would be invested to realize that yield. The term contract shown here is a 10-year renewable term policy requiring a premium for the age attained at the end of each renewal period.

In making this comparison, we have used present estimated figures of one of the low cost insurance companies. The difference in this example amounts to $4,715 for a $10,000 policy carried 30 years. From this it can be seen that if you carry a $50,000 life program over a period of 30 years, the saving would be $23,575, which illustrates the dramatic cost advantage of ordinary or whole life over term insurance. For this reason we recommend conversions from term to ordinary life insurance as early as possible, since each year of delay represents a definite dollar loss to you. It is our belief that term insurance can be used to definite advantage only for needs that will exist a relatively short period of time, or to enable a person to carry more insurance until such time as conversion is economically possible.

	Term Ins. to Age 65	*Ord. Life to Age 65*
30-year Premium Outlay	$6,903	$8,450
Assum. Div. Age 65		2,614
Cost of Insurance	$6,903	$5,836
Cash Value at Age 65		5,658
Insurance Cost to Age 65	$6,903	$ 178
Funds Available From Depositing Premium Difference to Earn 3 per cent	2,010	
Net Cost to Age 65	$4,893	$ 178

(Continued on page 197)

Mr. Wehrenberg is Missouri-Kansas manager, Professional Management Midwest, 4010 Washington Street, Kansas City, Missouri.



Washington HIGHLIGHTS

This summary of Washington news is prepared by the A.M.A. Washington Office for distribution to state medical journals.

Medical Care for Aged Ahead

Congress appears headed for a showdown this session on legislation for the Federal government to provide medical care for aged persons.

The medical profession and allied groups stepped up their activities in opposition to such legislation as indications mounted that the issue was approaching a crucial stage. Several State Medical Societies planned to send delegations to Washington to personally express their opposition to their Congressmen.

Pressure behind such legislation began to build up early in February.

The Eisenhower Administration announced it was working on three possible programs for providing health care for aged persons in cases of castastrophic —lengthy and costly—illness.

Possible Change

Without amplification, President Eisenhower told a news conference that there was under consideration "a possible change" in the Social Security Act "to run up the taxes by a quarter of a per cent to . . . make greater provision for the care of the aged." The President's statement that "there has been no conclusion reached in the administration" was backed up by Arthur S. Flemming, Secretary of Health, Education, and Welfare, in a clarifying announcement.

Flemming said his department was working on two other approaches to what he called a serious problem in addition to the possible revision of the Social Security law mentioned by Mr. Eisenhower. The HEW Secretary said consideration also was being given to: 1) stepped-up Federal assistance under the Federal-state public assistance program, and 2) the Federal government supplementing voluntary insurance programs.

Flemming again expressed opposition to the Forand bill which would increase Social Security taxes by one quarter of one per cent each on employers and employees to provide hospitalization, surgical benefits and nursing home care for Social Security beneficiaries. The Secretary said he wanted to "underline that the position of the administration is opposition to the Forand bill."

Flemming said he hoped to have an administration bill ready to submit in early April to the House Ways and Means Committee where the Forand bill is pending. The Committee is scheduled to take up in late March or early April proposed changes to the Social Security Act.

Proponents of the Forand bill—which is vigorously opposed by the American Medical Association and allied groups—were pointing their campaign toward securing the House Committee's approval of the legislation at that time.

Labor Favors Forand

The AFL-CIO, a main supporter of the Forand bill, urged labor union members to write to congressmen on the Committee urging them to vote for it. The AFL-CIO also distributed a pamphlet quoting a handful of physicians as supporting the legislation. But the labor organization didn't mention that the overwhelming majority of doctors oppose it.

McNamara Reports Findings

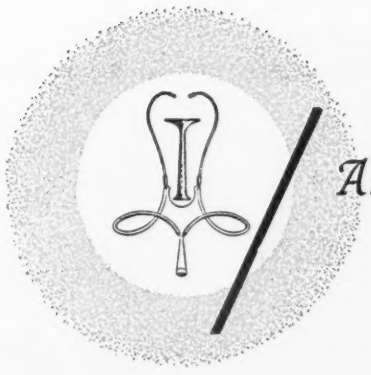
The Senate Subcommittee on Problems of the Aged and Aging, headed by Sen. Pat McNamara (D., Mich.), issued on behalf of its Democratic majority a report stating that use of the Social Security program "is the most efficient procedure for providing" health care for older persons.

The A.M.A. and the Subcommittee's Republican minority promptly disputed this conclusion. An A.M.A. statement issued in Chicago said:

"The American Medical Association today sharply disagreed with the recommendation of the McNamara subcommittee regarding government medicine for Social Security beneficiaries.

"Dr. Louis M. Orr, Orlando, Florida, President of the A.M.A., said: 'This is a politically inspired committee. Senator McNamara, Democrat from Michigan, has long supported political medicine. The fact is that at the seven subcommittee hearings held throughout the United States, observers heard little support expressed by the older citizens who attended the hearings for government medicine financed by additional taxes and administered through Social Security.' "

(Continued on page 197)



Announcements

Professional meetings, conferences, and postgraduate courses of national importance are listed for the* Doctor's Calendar. *Notice of the session is posted in advance to allow the physician time to make preparations.

The next scheduled examinations of the American Board of Obstetrics and Gynecology (Part II), oral and clinical for all candidates will be conducted at the Edgewater Beach Hotel, Chicago, Illinois, by the entire Board from April 11 through 16, 1960. Formal notice of the exact time of each candidate's examination will be sent him in advance of the examination dates.

Candidates who participated in the Part I Examinations will be notified of their eligibility for the Part II Examinations as soon as possible.

The deadline date for the receipt of New and Reopened Applications for the 1961 examinations is August 1, 1960. Candidates are urged to submit their applications as soon as possible before that time to Robert L. Faulkner, M.D., 2105 Adelbert Road, Cleveland 6, Ohio.

The German Medical Association, host for the XIVth General Assembly of The World Medical Association in Berlin, September 15-22, 1960, has requested that we extend to each of you its cordial invitation to attend this meeting. Special plans are already far advanced for this meeting. The German Medical Association has scheduled its own Annual Meeting in conjunction with the General Assembly and the opening and closing plenary sessions of the two organizations will be held together. Both meetings and all activities associated with them will be held in the new Berlin Convention Hall. This will facilitate attendance at those sessions of each meeting which are of most interest to the individual doctor. In addition to the regular features of each Annual Meeting, an International Film Program is scheduled during the entire period—its theme: Postgraduate Education.

The Annual Dinner on September 19 will be held at the world famous "Palais am Funkturm." The Excursion on September 22 will include a sightseeing tour through the East Sector of Berlin and will end with a cruise on Havel Lake.

The Business Side of Medicine

(Continued from page 195)

Ideal Combination

The ideal combination when beginning an insurance program is to use decreasing term riders such as family income and mortgage redemption. These riders fill the need for temporary or decreasing amounts of insurance at the least cost. However, to utilize these riders it is necessary to purchase permanent type policies, such as ordinary or whole life.

As a result of the tremendous difference in net costs between companies and types of policies, savings amounting to thousands of dollars can be realized over a lifetime by proper organization of your insurance program.

Washington Highlights

(Continued from page 196)

The Republican minority stated that testimony before the Subcommittee "proves that it is possible for elderly people to secure private insurance to provide hospitalization and surgical benefits without any intervention by public authorities."

Kennedy's Bill

Sen. John F. Kennedy (D., Mass.), a leading contender for the Democratic nomination for President, introduced legislation similar to the controversial Forand bill but broader in scope. The Kennedy bill would eliminate surgical benefits but would add diagnostic outpatient and home nursing services.

KMS Obituaries

CLYDE WILSON, M.D.

Dr. Clyde Wilson, 76, who has been a physician and surgeon in Emporia for 50 years, died January 17, in St. Mary's Hospital, after suffering a heart attack.

Dr. Wilson, the son of Newton and Frances Pamela Ridenour Wilson, was born November 13, 1884, on a farm near Lang. He was graduated from the medical school of University of Louisville, Kentucky, in 1909. He did graduate work at Johns Hopkins University, and had his surgical fellowship at the Mayo Clinic. In 1927 he was one of 104 doctors who spent two months in Europe doing postgraduate study under the sponsorship of Dr. Charles Mayo.

Among his survivors are his wife, a son, Clyde Newton Wilson; and a daughter, Dr. Barbara Wilson.

Dr. Wilson became a member of the Kansas Medical Society in 1938.

F. W. LEMON, M.D.

Dr. Frederick W. Lemon, 84, retired physician who had lived in Salina two years, passed away January 19 in the Asbury Hospital, two days after being admitted there for treatment. Death was ascribed principally to his advanced age.

Among his survivors are a daughter, Mrs. C. B. Gibson, three grandchildren, and two great-grandchildren.

Dr. Lemon was a member of the Masonic Lodge at Douglas, and Midian Shrine of Wichita.

He was born March 5, 1875, in Lincoln, Missouri. He graduated from the Beaumont Hospital Medical College at St. Louis, Missouri in 1901.

He was a member of the Butler County Medical Society and joined the Kansas Medical Society in 1933. His specialty was general practice.

E. H. DECKER, M.D.

Dr. Ernest H. Decker, 64, Topeka dermatologist, died January 26 in a Topeka hospital. He was stricken at his office in the Mills Building.

Dr. Decker was born July 20, 1895, at Girard and was graduated from the University of Missouri in 1922 and from the St. Louis University Medical School in 1924.

He came to Topeka in 1930 and became associated with the late Dr. Arthur D. Gray in the Mills Building.

He served his internship at St. Mary's Hospital in Kansas City and took special training under the late Richard L. Sutton in Kansas City. He served in the U. S. Army Medical Corps during World War I.

He was associated with the Santa Fe Hospital from 1930 to 1939 and was consultant at the Winter General Hospital during the war years.

He was a member of Grace Cathedral, a past president of the Shawnee County Medical Society and a member of the American Medical Association, Sigma Epsilon social fraternity, Phi Beta Pi medical fraternity, and Capitol Post No. 1, American Legion.

He is survived by his wife, Mrs. Grace Decker, three sons, Donald H. Decker, James B. Decker and Paul A. Decker, a daughter, Mrs. Jane Rodgers, and 10 grandchildren.

The first specific aldosterone-blocking agent...

ALDACTONE™

effectively extends the medical control of edema or ascites.
It introduces a new therapeutic principle in the treatment of...

CONGESTIVE HEART FAILURE • HEPATIC CIRRHOSIS
THE NEPHROTIC SYNDROME • IDIOPATHIC EDEMA

ALDACTONE introduces a new class of therapeutic agent, the aldosterone-blocking agent providing:

satisfactory relief of resistant or advanced edema even when all other agents, alone or in combination, are ineffective or are only partially effective.

A New Order of Therapeutic Activity

ALDACTONE acts by blocking the effect of aldosterone, the principal mineralocorticoid governing the reabsorption of sodium and water in the distal segment of the renal tubules.

By so doing Aldactone establishes a fundamentally new and effective approach to the control of edema or ascites, including edema resistant or unresponsive to conventional diuretic agents.

Further, because of its different site and mode of action in the renal tubules, Aldactone has a true, highly valuable synergistic activity when used with a mercurial or thiazide diuretic.

What Physicians May Expect of Aldactone

It is fully expected that Aldactone will change present medical concepts of the therapeutic limitations of managing edema. Many patients living in a greater or lesser state of edematous invalidism can now be edema-free. To others, gravely ill, Aldactone will be life-saving.

When used alone, Aldactone will produce a satisfactory diuresis in about half of those patients whose edema is resistant to conventional diuretic agents.

When Aldactone is used in a comprehensive therapeutic regimen, which includes a mercurial or a thiazide diuretic, a satisfactory diuresis and relief of edema may be expected in approximately 85 per cent of edematous patients *who would not otherwise respond.*

DOSAGE: For most adult patients the optimal dosage of Aldactone, brand of spironolactone, is 100 mg. four times daily. Aldactone should be administered for at least four or five days before appraising the initial response, since the onset of therapeutic effect is gradual when it is used alone. Aldactone manifests accelerated activity with greater response as early as the first and second days when used in combination with a mercurial or thiazide diuretic.

SUPPLIED: Aldactone is supplied as compression-coated yellow tablets of 100 mg.

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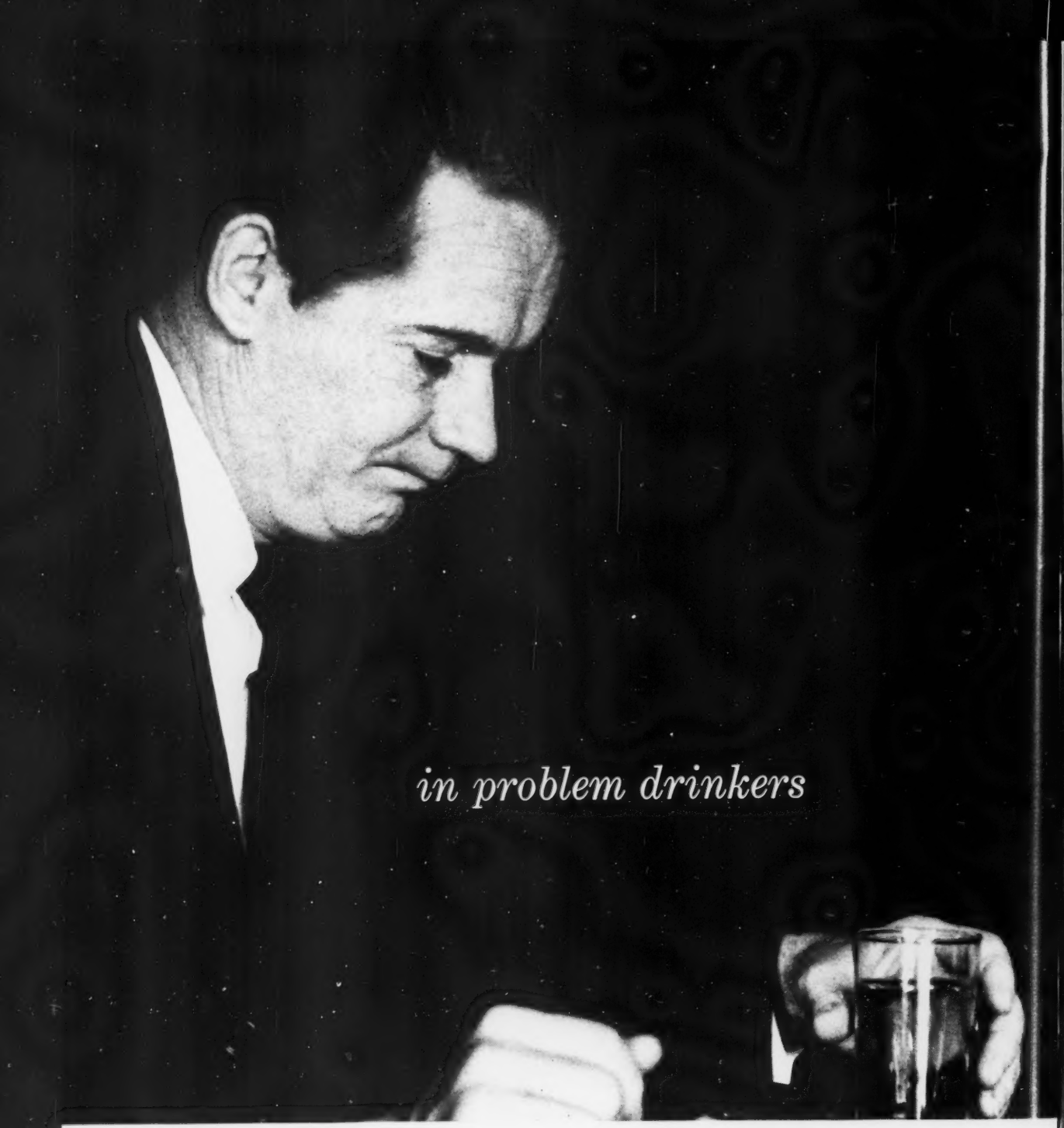

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dispels tension...
maintains tranquility

When tension and anxiety "drive him to drink," the problem drinker often finds that VISTARIL, by maintaining tranquility, restores perspective and helps him accept counsel more readily.

VISTARIL has demonstrated a wide margin of safety even in large doses (300-400 mg. daily) over prolonged periods. Clinical studies of alcoholism have shown that VISTARIL produces no significant depression of blood pressure, pulse rate, or respiration in chronic drinkers.

Capsules—25, 50, and 100 mg. *Parenteral Solution* (as the HCl)—25 mg. per cc., 10 cc. vials and 2 cc. Steraject® Cartridges; 50 mg. per cc., 2 cc. ampules.

Professional literature available on request from the Medical Department, Pfizer Laboratories, Div., Chas. Pfizer & Co., Inc., Brooklyn 6, New York

Pfizer *Science for the world's well-being*™

In vitro facts and in vivo findings on new broad-spectrum

DECLOMYCIN

PROPERTIES PERFORMANCE IMPORTANCE

A MAJOR CONTRIBUTION TO ANTI-INFECTIVE THERAPY

PROPERTIES:

Greater inhibitory action ...lower daily intake than other tetracyclines

A unique new fermentation product of *Streptomyces aureofaciens,* DECLOMYCIN Demethylchlortetracycline achieves notably greater antibiotic activity against infections[2,4,7,8,10,14,19,20,24] because of two basic factors: (1) inherent potency, and (2) greater stability in most body fluids.[15,17,18,27] Actual clinical activity has, in many instances, been better than expected on the basis of *in vitro* sensitivity tests.[14,18,19]

Broad-spectrum control ...with far less antibiotic

Activity levels of DECLOMYCIN Demethylchlortetracycline are higher than those of previous broad-spectrum antibiotics. Hardier strains of various organisms appear to be somewhat more responsive.[4] Apparently some strains of Pseudomonas, Proteus and *A. aerogenes,* frequently refractory to therapy, are sensitive to DECLOMYCIN.[7,23,25,26]

DECLO

PROPERTIES

Sustained peak activity ...greater security of control

Prolonged retention and compatibility of DECLOMYCIN with body fluids provides peak activity between doses.[15,17,18,27] Inhibition of bacteria is more constant.

24-48 hours extra activity...protection against relapse

DECLOMYCIN maintains effective antimicrobial action for one to two days after stopping dosage.[7,14] Resurgence of a few viable pathogens, with relapse...and low patient defense against secondary bacterial invasion during the first post-therapy days... are largely offset.

MYCIN®

Demethylchlortetracycline Lederle

PERFORMANCE

Susceptibility Tests

Roberts, M. S., *et al.*[25]
New York, N. Y.

Pre-treatment sensitivity tests in 75 genitourinary patients showed DECLOMYCIN Demethylchlortetracycline to be superior against the large majority of organisms and in no instance inferior to tetracycline. DECLOMYCIN apparently has more effective coverage... several strains of *Proteus* and *A. aerogenes* responded.

Tolerance & Toxicity

Boger, W. P., and Gavin, J. J.[2]
Norristown, Pa.

Administration of the recommended 600 mg. (4 capsules) daily for 30 days to a small group of elderly patients revealed no hematologic, hepatic and urinary alteration or other abnormal finding. No clinical side effects were observed.

Gonococcal Infection

Marmell, M., and Prigot, A.[20]
New York, N. Y.

All except two of 63 patients with acute gonorrhea responded promptly to therapy with DECLOMYCIN. Fifteen received 250 mg. q.i.d. for one day, the remainder received 600 or 750 mg. in divided doses over one or two days. No side effects.

General Medicine

Lichter, E. A., and Sobel, S.[19]
Chicago, Ill.

One hundred and sixty-nine patients with various infections showed generally equivalent response to four dosage regimens, including the recommended level. Of 29 pneumococcal pneumonias, all recovered with 15 afebrile in 48 hours or less – except a few patients with preterminal underlying disease. All 42 scarlet fever patients recovered with 32 afebrile in 48 hours or less. Other patients also responded satisfactorily with few exceptions. No blood, liver or kidney toxicity found. G.I. side effects occurred in only 2 per cent at the recommended dosage, or less, and were easily reversible.

Respiratory Infection

Perry, D. M., *et al.*[22]
Seattle, Wash.

Good or fair response in 24 of 30 cases of acute bacterial pneumonia, and in all of six cases of acute bronchitis. Side effects occurred at higher dosage but were uniformly absent when dosage was limited to 600 mg. per day.

Various Infections

Finland, M., *et al.*[7]
Boston, Mass.

Eighty patients with various infections were treated with DECLOMYCIN Demethylchlortetracycline and an equal number with tetracycline. Therapeutic response was indistinguishable between the two groups. However, DECLOMYCIN Demethylchlortetracycline dosage was much lower (50 to 60 per cent of that of tetracycline.) In addition, incidence of side effects with demethylchlortetracycline was only half that experienced with tetracycline.

Pyelonephritis

Vineyard, J. P., *et al.*[29]
Dallas, Tex.

Therapy with DECLOMYCIN was successful in 12 of 13 patients with pyelonephritis. Sterile cultures were obtained in nine patients within six to 14 days. Among the organisms suppressed were strains of *A. aerogenes, E. coli* and paracolon bacillus. In most cases, DECLOMYCIN was used jointly with another antibiotic.

Soft Tissue Infection

Prigot, A., *et al.*[24]
New York, N. Y.

DECLOMYCIN was used alone or auxiliary to surgical measures in 150 cases of acute soft tissue infection, mostly ambulatory. Full resolution of infection was achieved in all cases, average length of treatment being six days. Dosage was 600 or 750 mg. daily. Side effects consisted of transitory G.I. disturbances in three cases.

DECLO

Urinary Infection

Trafton, H. M., and Lind, H. E.[28]
Brookline, Mass.

Clinical response was favorable in a majority of 50 cases of urinary tract infections with relief of symptoms, elimination, or marked reduction, of pyuria and with urine sterilization in some. DECLOMYCIN Demethylchlortetracycline was administered in one-half to one-third the daily milligram level of related antibiotics, for 8 days.

No significant diarrhea occurred in any case although mild nausea and upper G.I. symptoms were fairly common. Phototoxicity occurred in six cases.

Antibiotic-Resistant Infections

Compilation of reports of 210 clinical investigators.[23]

In 570 treated for a great variety of infections, DECLOMYCIN was successful in resolving infection or in effecting marked improvement in 81 per cent, after failure of other antibiotics.

Pediatric Infection

Fujii, R., *et al.*[9]
Tokyo, Japan

Therapeutic results, elicited in 309 pediatric patients with average daily dosage of 15 mg./kg., were equal to those produced by 30 mg./kg. of buffered tetracycline preparations. Satisfactory results were obtained in 75 per cent. No appreciable side effects when 15 mg./kg./day dosage was not exceeded.

Pediatric Infection

Hall, T. N.[12]
San Francisco, Cal.

All eight cases of ophthalmic, respiratory or otic infection responded to four to twelve days of DECLOMYCIN therapy (5 recovered, 2 greatly improved, 1 improved). One skin reaction, in a case receiving the higher trial dosage of 7 mg./lb. daily, occurred.

Pneumonias

Duke, C. J., *et al.*[5]
Washington, D. C.

Results were satisfactory in all 32 cases of acute bacterial penumonia, excepting for two caused by non-susceptible organisms. Over half had been complicated by pleural, suppurative, bronchial, or underlying structural lung problems. Dosage was low. No toxicity found. Acceptance and toleration were excellent.

Intestinal & Respiratory Infection

Hartman, S. A.[13]
Sherman Oaks, Cal.

Six cases of g.i. infection (diverticulitis, ileitis, colitis) responded in three to eight days on the lower milligram intake... even after failure in most with sulfa, neomycin or penicillin-streptomycin. Complete recovery was gained in 5 respiratory cases on a shorter schedule; another withdrew with occurrence of thrush. No other side effects were reported.

Respiratory Infection

Feingold, B. F.[6]
San Francisco, Cal.

All 13 upper or lower respiratory infections demonstrated very good response in 2-3 days on recommended dosage. No side effects were reported.

Various Infections

Compilation of reports of 210 clinical investigators.[23]

Of 1,904 patients with adequate follow-up treated for a wide diversity of infections, 87 per cent were reported as cured or improved. Most patients received one 150 mg. tablet every 6 hours. Therapy usually was for three to eight days. Side effects, mostly referable to the gastrointestinal tract, occurred in 200 patients.

PERFORMANCE

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Demethylchlortetracycline Lederle

PERFORMANCE *(continued)*

Respiratory Infection & Others

Gates, G. E.[11]
South Bend, Ind.

Of 65 cases, predominantly respiratory infections, but including some of cystitis and cellulitis, 50 had a good response, 12 were fair and three were failures. One of the failures was a case of chronic ulcerative colitis and two were respiratory infections. The only complication was a slight vulvular pruritus and burning tongue occurring near the end of a week's treatment of residual pneumonitis.

Pustular Dermatoses

Kanof, N. B., and Blau, S.[16]
New York, N. Y.

Eighty-five per cent of 67 patients responded with excellent or good results on a DECLOMYCIN schedule of one 150 mg. capsule q.i.d. for two to twelve weeks. Three poor responses were related to highly resistant organisms. No pruritus or drug eruptions developed. Only four cases showed nausea or diarrhea in the long therapeutic course.

Surgical Infection

Floyd, R. D., and Anlyan, W. G.[8]
Durham, N. C.

Successful results were generally obtained in 60 patients given 600 mg. DECLOMYCIN daily (or slightly less) for five to 15 days. No infection developed in the clean or contaminated prophylaxis group. Most frank infections responded...including several refractory to previous antibiotics. No toxicity evidenced. Intestinal toleration was excellent.

Wound Infections & Others

Meyer, B. S.[21]
Birmingham, Ala.

Thirty-five cases, chiefly prophylactic, and some traumatic-surgical wound infections were treated usually on one capsule DECLOMYCIN q. 6 h. for two to eight days. Over 80 per cent responded, including one with Pseudomonas etiology. Minor itching or nausea occurred in two; prominent nausea developed in one on a q. 4 h. schedule.

Topical & Wound Infections

Stewart, J.[20]
New Orleans, La.

Of 21 patients followed, 15 completely recovered, four improved in four to 42 days on 600 mg. daily. Seven had not responded to various other therapies. One had *A. aerogenes* predominance, complicated by Proteus and *E. coli*. Cases were traumatic-surgical-topical infections with some respiratory. One questionable reaction of anemia was encountered.

Oral Infection

Arbour, E. F.[1]
New Orleans, La.

Of four patients treated, three responded to one capsule DECLOMYCIN q. 6 h. for three days. No change in one case of chronic proliferating periodontitis. No adverse reactions seen.

Brucellosis

Chávez, Max, G.[3]
Mexico, D. F.

All nine patients infected with *Brucella melitensis* were afebrile on fourth or fifth day of DECLOMYCIN therapy and asymptomatic within 15 days. Treatment lasted for 45 days. No relapses occurred. Hepatic, renal, or hematologic toxicity was not seen. Minor or occasional intestinal reactions in some cases did not require discontinuance.

DECLO

IMPORTANCE...

in the average patient – DECLOMYCIN reduces the possibility of gastrointestinal intolerance and increases the likelihood of an uneventful therapeutic course. Variants of an infecting organism are less likely to survive the high, sustained activity and post-dosage control. Minor or major reverses or "setbacks" during therapy may be avoided. Susceptibility to secondary infection when dosage is terminated is counteracted by the "extra-day" activity.

in mixed infections–DECLOMYCIN provides satisfactory control of conditions involving multiple pathogens. Since organisms vary in sensitivity at given antibiotic levels, the higher DECLOMYCIN activity tends to inhibit a greater proportion of the less susceptible strains. Remission and bacteriologic cure can thus progress at a faster pace.

in the absorption-deficient – The high activity/intake ratio of DECLOMYCIN provides a wider margin of security for those with disturbed or abnormal absorption or with underlying gastrointestinal dysfunction. Inhibitory levels remain more than adequate in most.

under adverse host conditions– In debility, malnutrition, neoplasm, diabetes, or other organic, chronic or underlying disease, DECLOMYCIN may be vital to successful resolution of infection. *Generally in geriatrics,* for the same reason, DECLOMYCIN should often be a broad-spectrum of choice.

if an occasional dose is missed – The sustained action of DECLOMYCIN protects against possible loss of control. In the sleeping patient, an occasional dose may be foregone without adverse effect, while benefits of such rest are gained. Arbitrary rejection of a dose by pediatric or geriatric patients... simple forgetfulness...or postponing a dose will not appreciably reduce antibiotic activity provided these do not occur frequently.

IMPORTANCE

MYCIN®

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a masterpiece of antibiotic design

CAPSULES, 150 mg., bottles of 16 and 100. *Dosage:* Average adult 1 capsule four times daily.

PEDIATRIC DROPS, 60 mg./cc. (custard flavor) in 10 cc. bottle with calibrated dropper. *Dosage:* 1-2 drops (3-6 mg.) per pound body weight per day—divided into 4 doses.

ORAL SUSPENSION, 75 mg./5 cc. teaspoonful (custard flavor) in 2 oz. bottle. *Dosage:* 3-6 mg./lb./day—divided in 4 doses.

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FOR SIMULTANEOUS IMMUNIZATION AGAINST 4 DISEASES:

Poliomyelitis-Diphtheria-Pertussis-Tetanus

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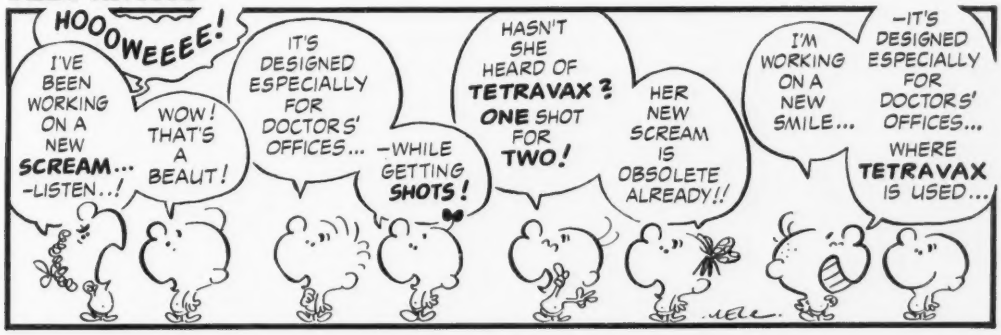
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Dose: 1 cc.
Supplied: 9 cc. vials in *clear plastic* cartons. Package circular and material in vial can be examined without damaging carton. Expiration date is on vial for checking even if carton is discarded.

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SQUIBB HYDROXYPROGESTERONE CAPROATE

Improved Progestational Therapy

Garden City, N. Y.

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DELALUTIN offers these advantages over other progestational agents

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Complete information on administration and dosage is supplied in the package insert

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"DELALUTIN"® IS A SQUIBB TRADEMARK

When blood pressure must come down

When you see symptoms of hypertension such as dizziness, headache, and fainting your patient is a candidate for Serpasil-Apresoline. Even when single-drug therapy fails, Serpasil-Apresoline frequently can bring blood pressure down to near-normal levels, reduce rapid heart rate, allay anxiety.

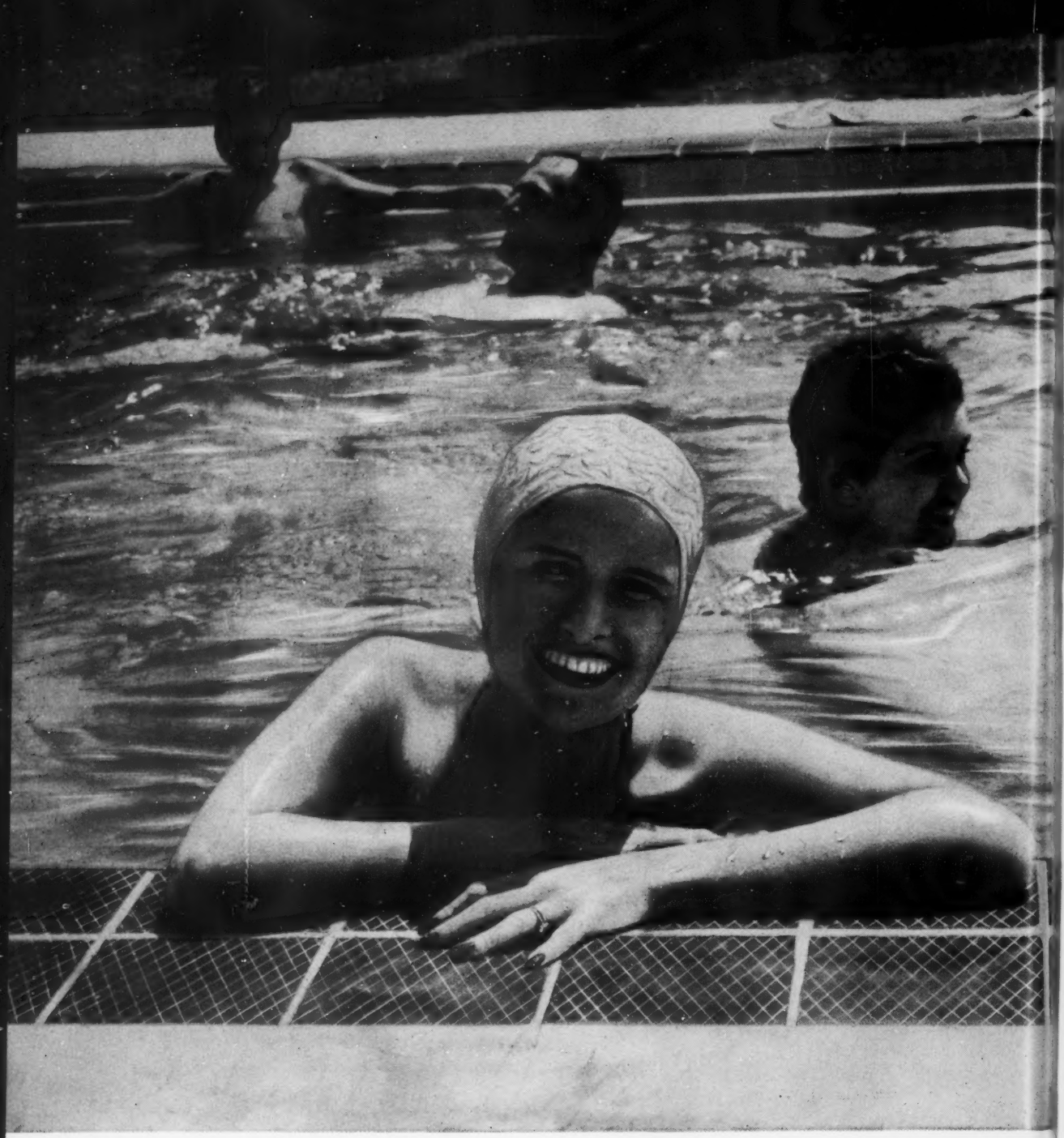
SUPPLIED: Tablets #2 (standard-strength, scored), each containing 0.2 mg. Serpasil and 50 mg. Apresoline hydrochloride; Tablets #1 (half-strength, scored), each containing 0.1 mg. Serpasil and 25 mg. Apresoline hydrochloride.

SERPASIL®-APRESOLINE®

hydrochloride (reserpine and hydralazine hydrochloride CIBA)

CIBA
SUMMIT, N. J.

2/2765MK



Of course, women like "Premarin"®

THERAPY for the menopause syndrome should relieve not only the psychic instability attendant the condition, but the vasomotor instability of estrogen decline as well. Though they would have a hard time explaining it in such medical terms, this is the reason women like "Premarin."

The patient isn't alone in her devotion to this natural estrogen. Doctors, husbands, and family all like what it does for the patient, the wife, and the homemaker.

When, because of the menopause, the psyche needs nursing—"Premarin" nurses. When hot flushes need suppressing, "Premarin" suppresses. In short, when you want to treat the whole menopause, (and how else is it to be treated?), let your choice be "Premarin," a complete natural estrogen complex.

"Premarin," conjugated estrogens (equine), is available as tablets and liquid, and also in combination with meprobamate or methyltestosterone.

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in every arthritic state
long-term therapy
with maximum relief of pain
without steroids

Buffered
Pabirin®
Tablets
improved salicylate therapy

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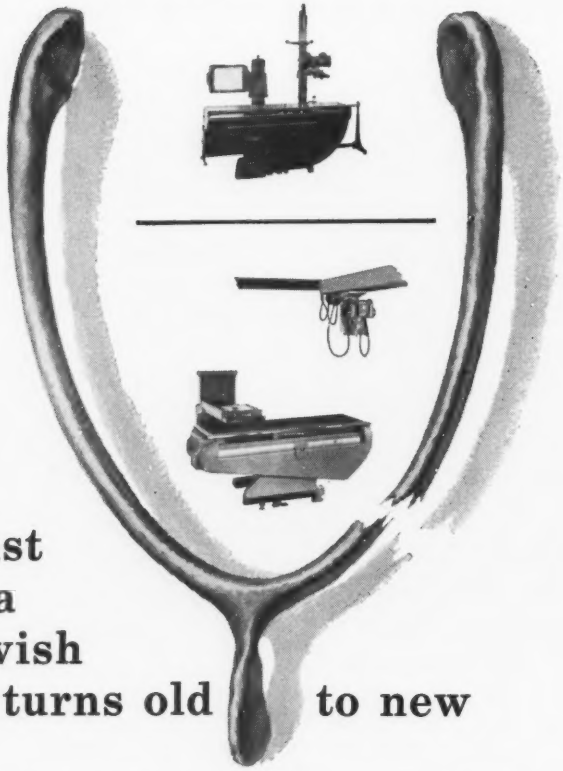

Just a wish turns old to new

Modernize without capital outlay on the G-E Maxiservice® x-ray rental plan

Think of renting x-ray equipment as conveniently as you subscribe for telephone service! Exclusive Maxiservice rental plan offers all new-model G-E x-ray units . . . takes no capital from your savings. Makes it worry-free to "go modern" in x-ray and always stay that way. For complete details, contact your G-E x-ray representative, listed below.

All this for one monthly fee —

- Modern x-ray equipment, free of obsolescence worries
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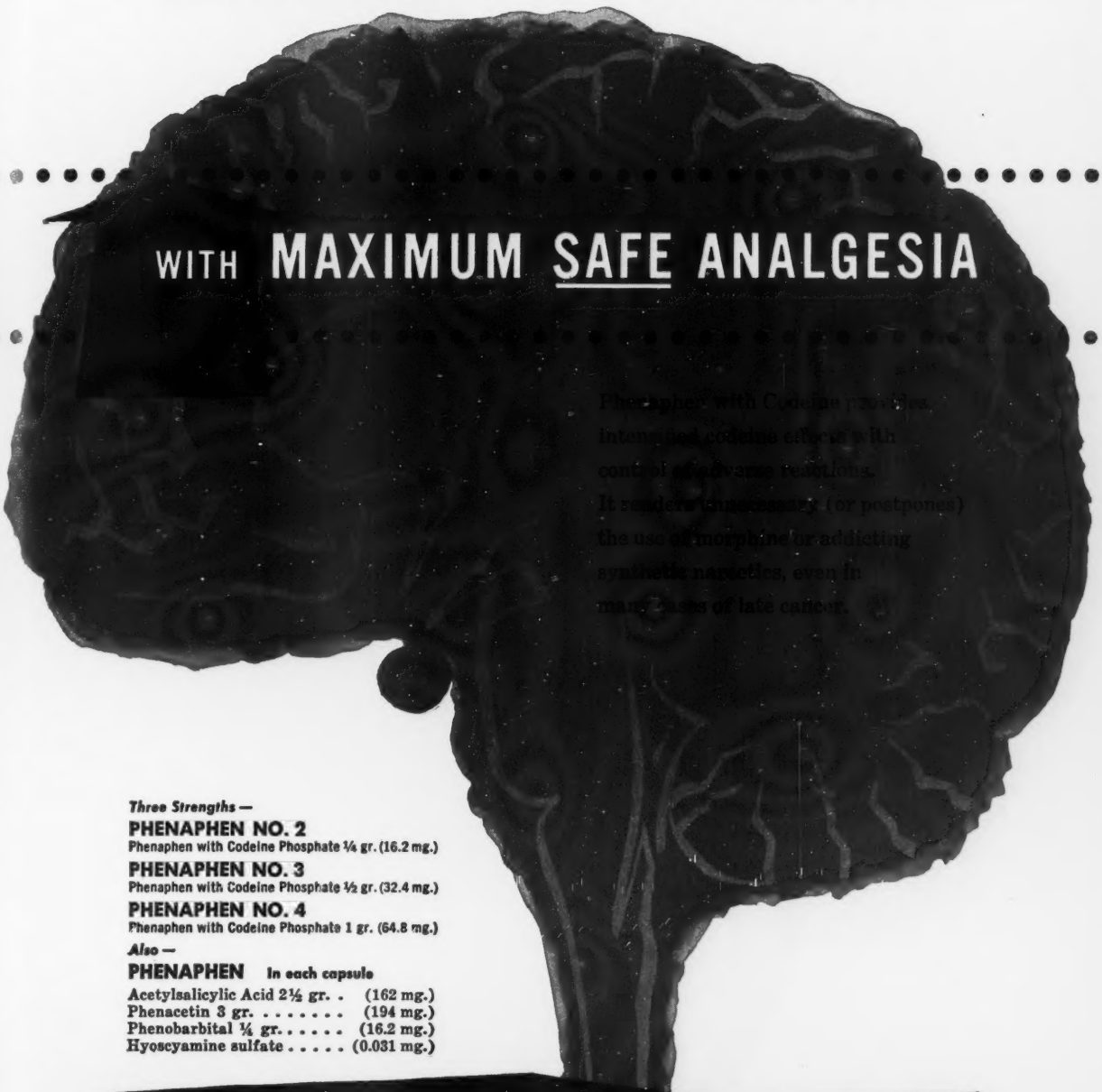

WITH MAXIMUM SAFE ANALGESIA

Phenaphen with Codeine provides intensified codeine effect with control of adverse reactions. It renders unnecessary (or postpones) the use of morphine or addicting synthetic narcotics, even in many cases of late cancer.

Three Strengths —

PHENAPHEN NO. 2
Phenaphen with Codeine Phosphate ¼ gr. (16.2 mg.)

PHENAPHEN NO. 3
Phenaphen with Codeine Phosphate ½ gr. (32.4 mg.)

PHENAPHEN NO. 4
Phenaphen with Codeine Phosphate 1 gr. (64.8 mg.)

Also —

PHENAPHEN In each capsule

Acetylsalicylic Acid 2½ gr. . (162 mg.)
Phenacetin 3 gr. . . . . (194 mg.)
Phenobarbital ¼ gr. . . . . (16.2 mg.)
Hyoscyamine sulfate . . . . . (0.031 mg.)

PHENAPHEN® WITH CODEINE Robins

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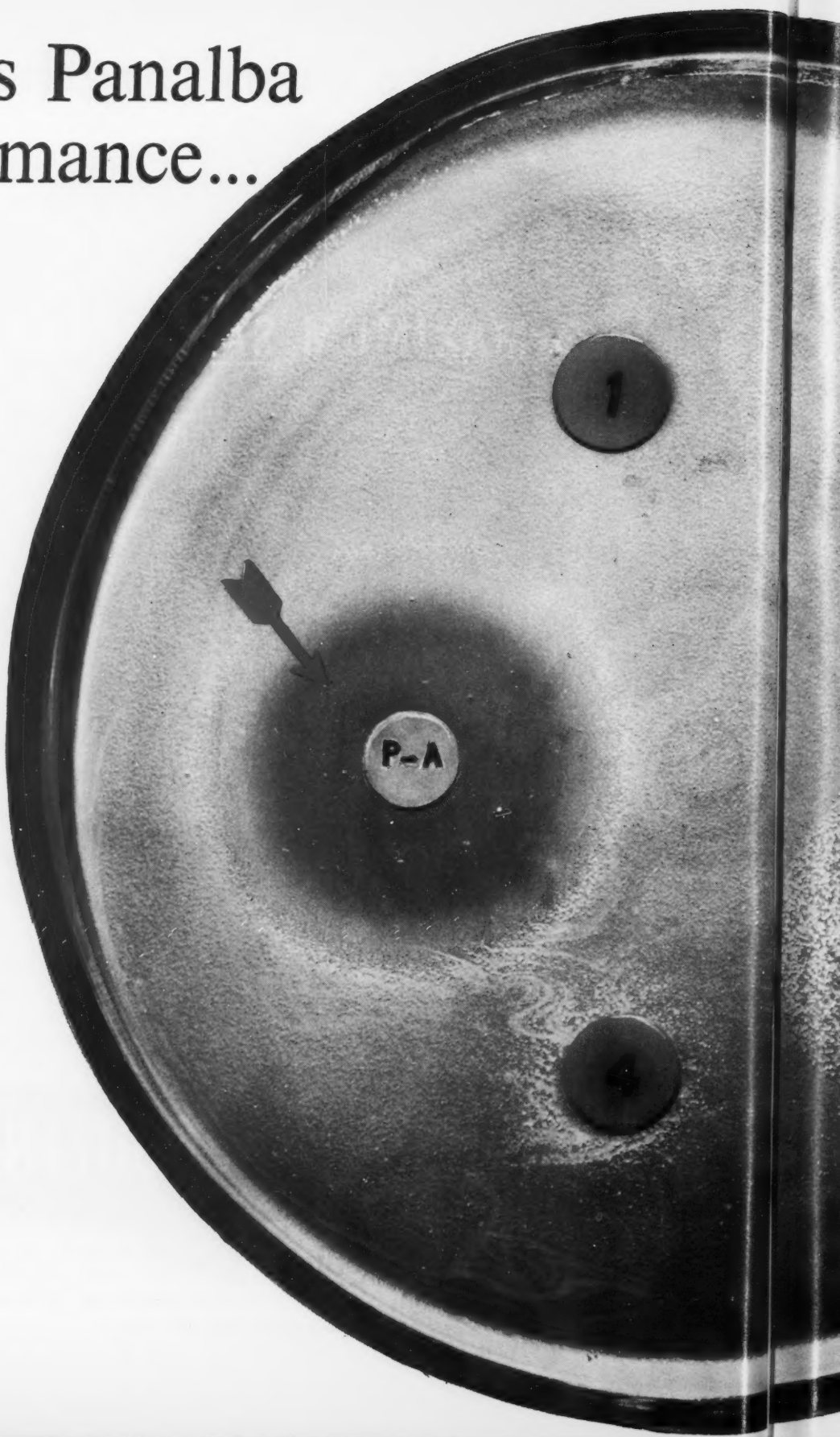
A. H. ROBINS CO., INC., RICHMOND 20, VIRGINIA

Ethical Pharmaceuticals of Merit since 1878

This is Panalba performance...



in pneumonia

. . . into a mixed culture of the three organisms commonly involved in pneumonia . . . *K. pneumoniae*, *Diplococcus pneumoniae*, and *Staphylococcus aureus* (in this case a resistant strain) . . . we introduce the five most frequently used antibiotics.

Twenty-four hours later (in this greatly enlarged photograph), note that only *one* of the five leading antibiotics has stopped *all* the organisms, including the resistant staph! This is Panalba.

In your next pneumonia patient . . . in *all* your patients with potentially-serious infections . . . provide this extra protection with your prescription:

Dosage—1 or 2 capsules 3 or 4 times a day. Supplied—Capsules containing Panmycin phosphate equivalent to 250 mg. tetracycline hydrochloride, and 125 mg. Albamycin as novobiocin sodium, in bottles of 16 and 100. *Now available:* new Panalba Half-Strength Capsules in bottles of 16 and 100.

Panalba*

(Panmycin* Phosphate plus Albamycin*)

The broad-spectrum antibiotic of *first* resort

Upjohn The Upjohn Company Kalamazoo, Michigan

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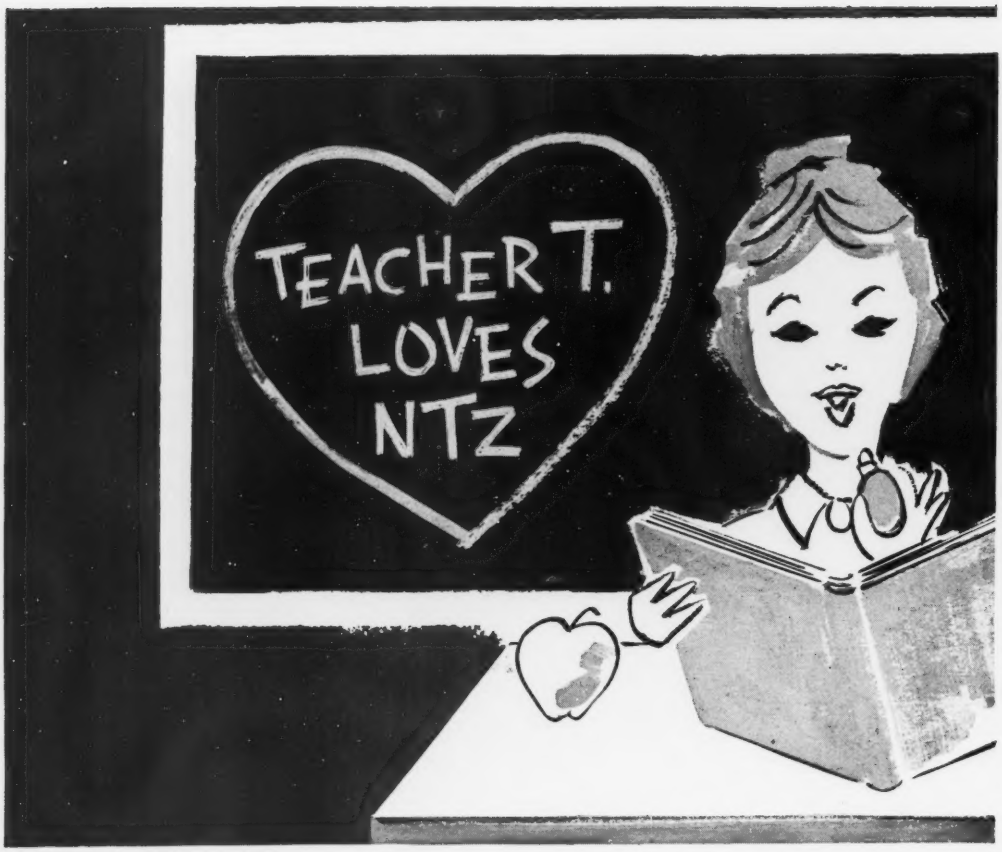

**In her book,
the lasting relief from colds
puts NTZ Nasal Spray
in a class by itself.**

NTZ® NASAL SPRAY

*20 cc. spray bottles;
also 1 oz. bottles with dropper*

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Neo-Synephrine® HCl, 0.5%
—unexcelled decongestant—

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—topical antihistaminic—

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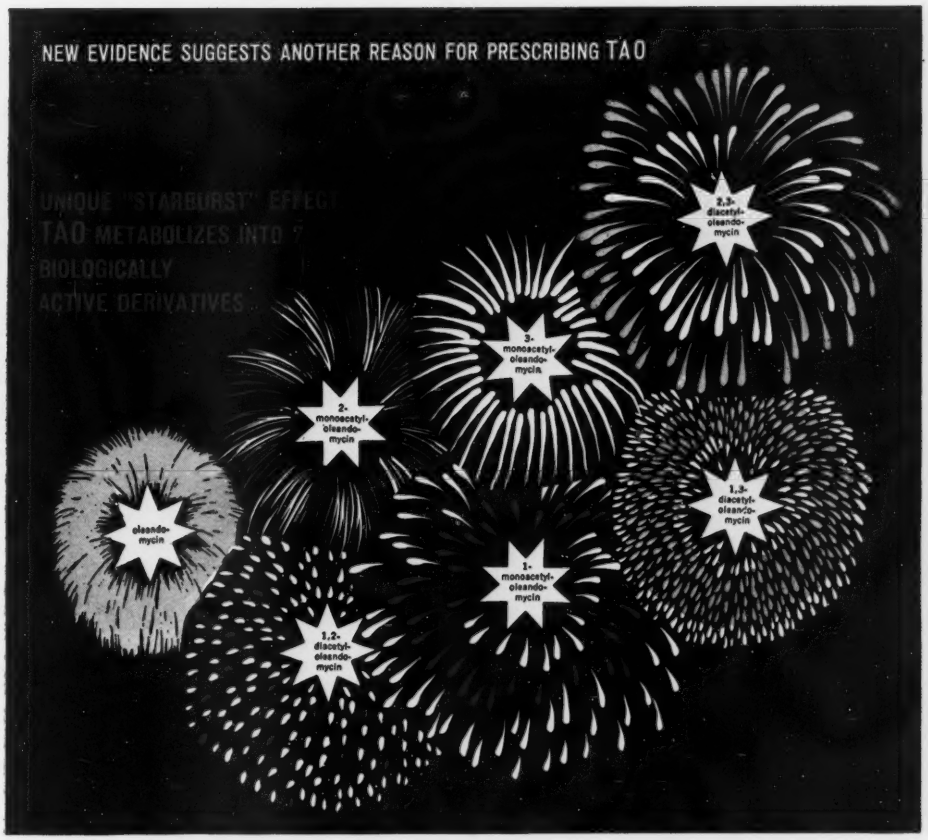
NTZ, Neo-Synephrine (brand of phenylephrine), Thenfadil (brand of thenyldiamine) and Zephiran (brand of benzalkonium, as chloride, refined), trademarks reg. U. S. Pat. Off.

Potentiated Relief for Colds...Sinusitis...Hay Fever



The impression that TAO is an unusually active antibiotic has steadily gained recognition by impressive clinical performance. Now come reports of **in vivo** and **in vitro** biological and biochemical evaluations that show TAO to be indeed unique.[1,2]

TAO differs from other antibiotics in that it is metabolized to multiple active compounds which **remain** active throughout their presence in the body. These 7 derivatives (in addition to TAO) show activity against common Gram-positive pathogens, including resistant strains of **Staph. aureus.**

In light of these findings, take another look at TAO performance: • 92% success in published cases of Gram-positive respiratory, skin, soft tissue and genitourinary infection • Effective against 78% of 64 "antibiotic-resistant" epidemic staphylococci. (In the same study, chloramphenicol was active against 52%; erythromycin against only 25%)[3] • No side effects in 94%; infrequent reactions mild and easily reversed • Quickly absorbed • Highly palatable.

Sound reasons to: Start with TAO to end 9 out of 10 common Gram-positive infections.

Supplied: TAO Capsules—250 mg., and 125 mg., bottles of 60. **TAO for Oral Suspension**—125 mg. per tsp. (5 cc.) when reconstituted; unusually palatable cherry flavor; 60 cc. bottle. Prescription only.

Other TAO forms available: TAO Pediatric Drops: flavorful, easy to administer. **TAO®-AC:** TAO analgesic, antihistaminic compound. **TAOMID®:** TAO with triple sulfas. **Intramuscular or Intravenous:** in clinical emergencies. Prescription only.

1. English, A. R., and McBride, T. J.: Proc. Soc. Exper. Biol. & Med. 100:880 (Apr.) 1959. 2. Celmer, W. D.: Antibiotics Annual 1958-1959, New York, Medical Encyclopedia, Inc., 1959, p. 277. 3. English, A. R., and Fink, F. C.: Antibiotics & Chemother. 9:420 (Aug.) 1958.

designed for superior control of common Gram-positive infections

TAO®

(triacetyloleandomycin)

Capsules/Oral Suspension

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Science for the World's Well-Being

BAD DIGESTION INCLINES ONE TO SKEPTICISM, INCREDULITY, BREEDS BLACK FANCIES AND THOUGHTS OF DEATH JOSEPH CONRAD

When bad digestion is the consequence of digestive enzyme deficiency, Entozyme may dispel dreary symptoms such as pyrosis, flatulence, belching, and nausea, for it is a natural supplement to digestive enzymes. It provides components with digestive enzyme activity: **Pepsin,** N. F., 250 mg., **Pancreatin,** N. F., 300 mg., and **Bile Salts,** 150 mg. Because Entozyme is actually a tablet-within-a-tablet, these components are freed in the physiological areas where they occur naturally. Entozyme has proved useful in relieving many symptoms associated with cholecystitis, post-cholecystectomy syndrome, sub-total gastrectomy, pancreatitis, infectious hepatitis, and a variety of metabolic diseases.

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ENTOZYME®

FIORINAL®

relieves pain,
muscle spasm,
nervous tension

rapid action • non-narcotic • economical

"We have found caffeine, used in combination with acetylsalicylic acid, acetophenetidin, and isobutylallylbarbituric acid, [Fiorinal] to be one of the most effective medicaments for the symptomatic treatment of headache due to tension."

Friedman, A. P., and Merritt, H. H.: J.A.M.A. *163*:1111 (Mar. 30) 1957.

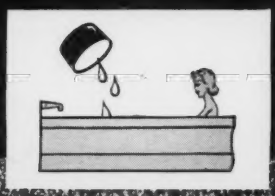
Fiorinal — available as tablets and *capsules* (new form). *Each contains:* Sandoptal (Allylbarbituric Acid N.F. X) 50 mg. (¾ gr.), caffeine 40 mg. (⅔ gr.), acetylsalicylic acid 200 mg. (3 gr.), acetophenetidin 130 mg. (2 gr.).

***Dosage:* 1 or 2 every 4 hours, according to need, up to 6 per day.**

SANDOZ

proven successful[1] in almost every case of

skin itch



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Used in the bath SARDO releases millions of microfine water-dispersible globules* to provide a soothing, softening suspension which enhances your other therapy. SARDO baths . . .

1 **rehydrate the dry, itchy, scaly skin**

2 **add comfort to the therapeutic care**

3 **act to measurably increase natural emollient skin oil**

4 **minimize loss of natural oil and excessive moisture with a fine non-occlusive film**

Patients will appreciate pleasant, convenient, easy to use, pine-scented SARDO. Non-sensitizing. Most economical. Bottles of 4, 8 and 16 oz.

1. Spoor, H. J.: N. Y. State J. Med. Oct. 15, 1958

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for atopic dermatitis
eczematoid dermatitis
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Samples and literature yours for the asking.

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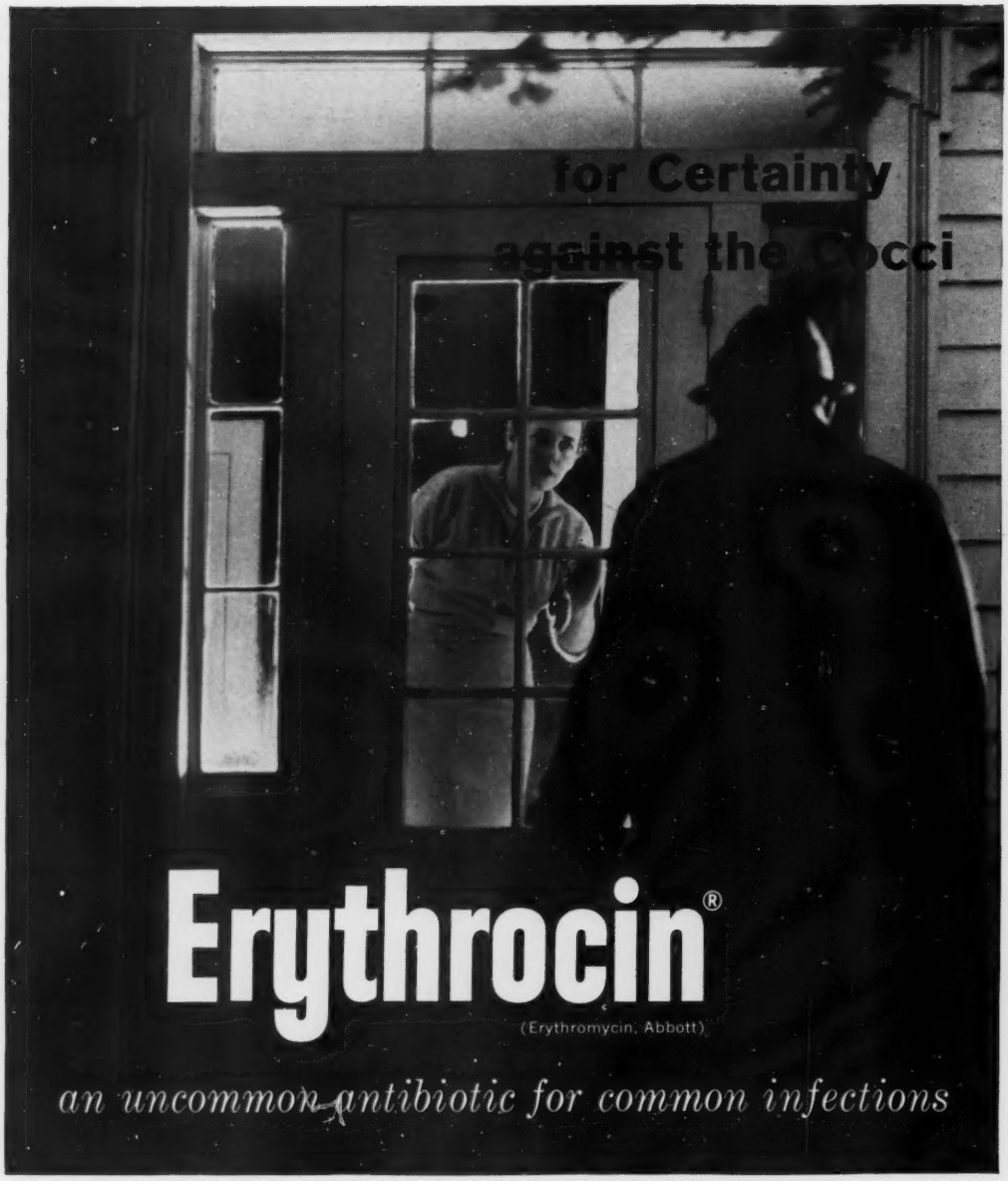
Trilafon® perphenazine for the anxiety in the person overwhelmed by family illness...selective anxiety relief with minimal drowsiness or dulling

S-419



Provides fast, high blood and tissue concentrations—plus an unparalleled safety record. Erythrocin is available in easy-to-swallow Filmtabs® (100 and 250 mg.); in tasty, citrus-flavored Oral Suspension (200 mg. per 5-cc. teaspoonful); and for intravenous and intramuscular use.

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THE FIRST TRUE "TRANQUILAXANT"

Trancopal®

relieves painful muscle spasm and relaxes the patient

Impressive numbers of patients with low back pain and other musculospastic conditions treated with Trancopal have been freed of symptoms and enabled to return to their usual activities, according to newly published clinical reports. In a recent study by Lichtman,[1] Trancopal brought excellent to satisfactory muscle relaxation to 817 of 879 patients. The patients in this group suffered from skeletal muscle spasm associated with low back pain (361 cases), stiff neck (128 cases), bursitis (177 cases), and other skeletal muscle disorders (213 cases). Side effects were rare (2 per cent of patients), and it was not necessary to discontinue medication in any of the patients. Lichtman comments: "Chlormethazanone [Trancopal] not only relieved painful muscle spasm, but allowed the patients to resume their normal activities with no interference in performance of either manual or intellectual tasks."[2]

When you prescribe Trancopal for musculoskeletal disorders, you can confidently expect that your patients will be relieved of the pain and stiffness. You can be sure of their speedy return to everyday work and recreation.

Mullin and Epifano call Trancopal "...a very effective skeletal muscle spasmolytic."[3] They found that Trancopal brought good to excellent relief to all of 39 patients with skeletal muscle spasm related to trauma, bursitis, rheumatoid arthritis, osteoarthritis, and intervertebral disc syndrome. (No side effects were noted except that one patient had slight dryness of the mouth.)

The pattern is similar in every new series reported: Ganz,[4] DeNyse,[5] Shanaphy[6] and Stough.[7]

Trancopal is a true "tranquilaxant"

Trancopal "...combines the properties of tranquilization and skeletal muscle relaxation with no concomitant change in normal consciousness."[6]

Relieves dysmenorrhea

Trancopal not only is valuable in treating patients with low back pain and other musculoskeletal disorders, but is also very effective in bringing relief from menstrual cramps and discomfort. Shanaphy suggests that Trancopal may help the patient by its combination of muscle relaxant and tranquilizing actions, and he finds that "...the continued use of chlormezanone [Trancopal] as a therapeutic agent in dysmenorrhea is advisable."[6] Trancopal was effective in 82 per cent of his series of 50 patients. In another study, which dealt with 52 adolescent girls and 23 women, Stough[7] reported that Trancopal gave complete or moderate relief in 86.4 per cent.

Alleviates tension

And, of course, Trancopal is also very useful in the treatment of patients in anxiety and tension states. As Ganz says, "...a most valuable drug for relieving tension, apprehension and various psychogenic states...allows the patient to use his energies in a more productive manner in overcoming his basic problems."[4]

Trancopal

a true "tranquilaxant"

that relieves skeletal muscle spasm and relaxes psychogenic tension without troublesome side effects, and keeps the patient on the job.

Indicated for...

Musculoskeletal disorders		Psychogenic disorders
Low back pain (lumbago)	Fibrositis	Anxiety and tension states
Neck pain (torticollis)	Ankle sprain, tennis elbow	Dysmenorrhea
Bursitis	Myositis	Premenstrual tension
Rheumatoid arthritis	Postoperative muscle spasm	Asthma
Osteoarthritis		Angina pectoris
Disc syndrome		Alcoholism

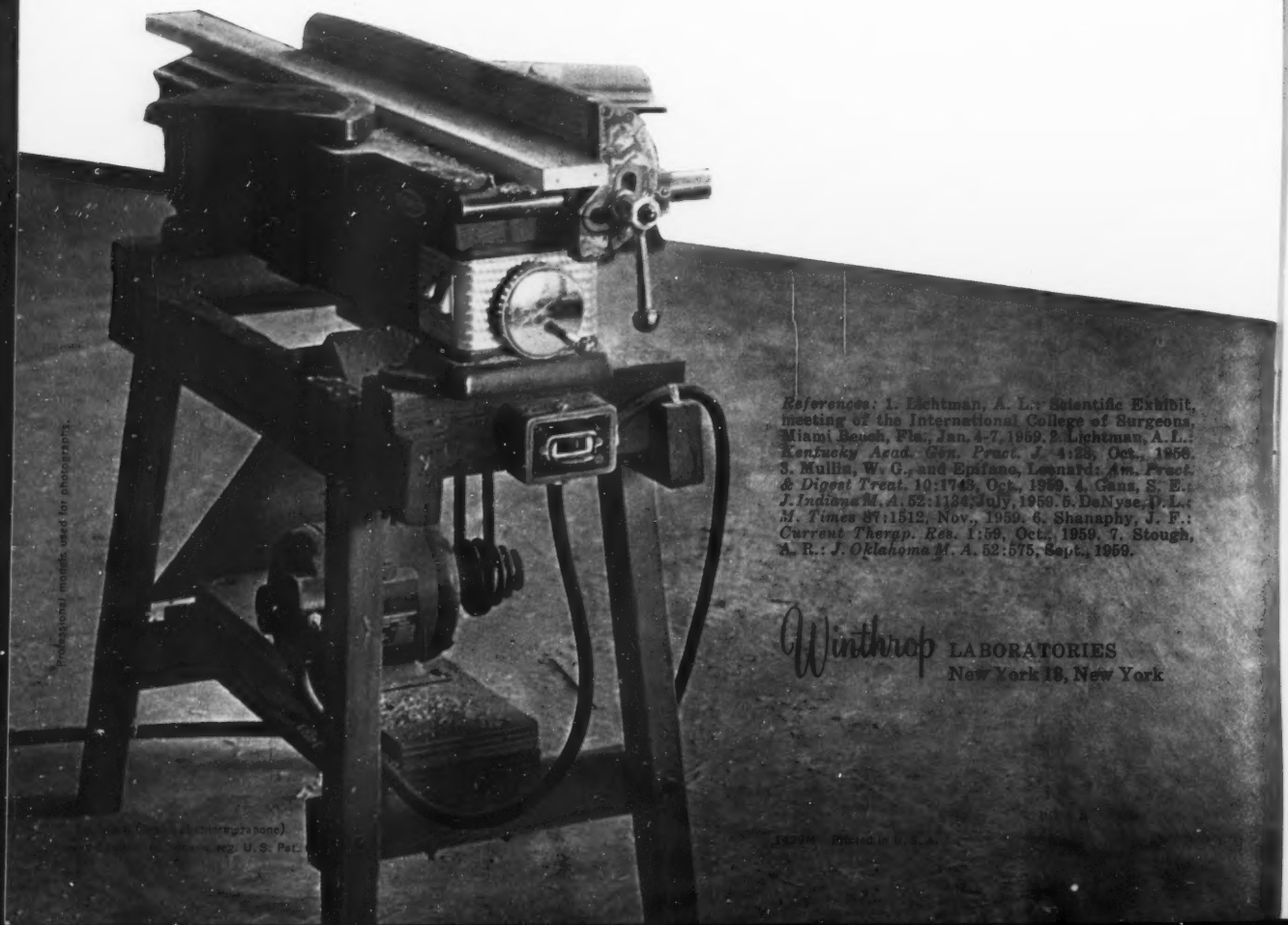
Now available in two strengths:

Trancopal Caplets®, 100 mg. (peach colored, scored), bottles of 100.

NEW STRENGTH

Trancopal Caplets, 200 mg. (green colored, scored), bottles of 100.

Dosage: Adults, 100 or 200 mg. orally three or four times daily. Relief of symptoms occurs in from fifteen to thirty minutes and lasts from four to six hours.



Professional models used for photographs.

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Incremin®
Lysine-Vitamins Lederle
with iron Syrup
for the undersized underweight child
build appetite
with
B complex
vitamins
prevent nutritional anemia
with ferric pyrophosphate, a form of iron exceptionally well-tolerated
promote protein uptake
with the potentiating effect of l-Lysine on low-grade protein foods
in taste-tempting cherry flavor
Average dosage, 1 teaspoonful (5 cc.) contains:
l-Lysine HCl . . . . . 300 mg.
Vitamin B12 Crystalline . . . 25 mcgm.
Thiamine HCl (B1) . . . . . 10 mg.
Pyridoxine HCl (B6) . . . . . 5 mg.
Ferric Pyrophosphate (Soluble) 250 mg.
Iron (as Ferric Pyrophosphate) 30 mg.
Sorbitol . . . . . 3.5 Gm.
Alcohol 75%
Bottles of 4 and 16 fl. oz.

Lederle LEDERLE LABORATORIES, a Division of AMERICAN CYANAMID COMPANY, Pearl River, New York

Lifts depression...

You see an improvement within a few days
Thanks to your prompt treatment and the quick, smooth action of Deprol, her depression is relieved and her anxiety and tension calmed – *often in a few days.* She eats well, sleeps well and soon returns to her normal activities.

as it calms anxiety!

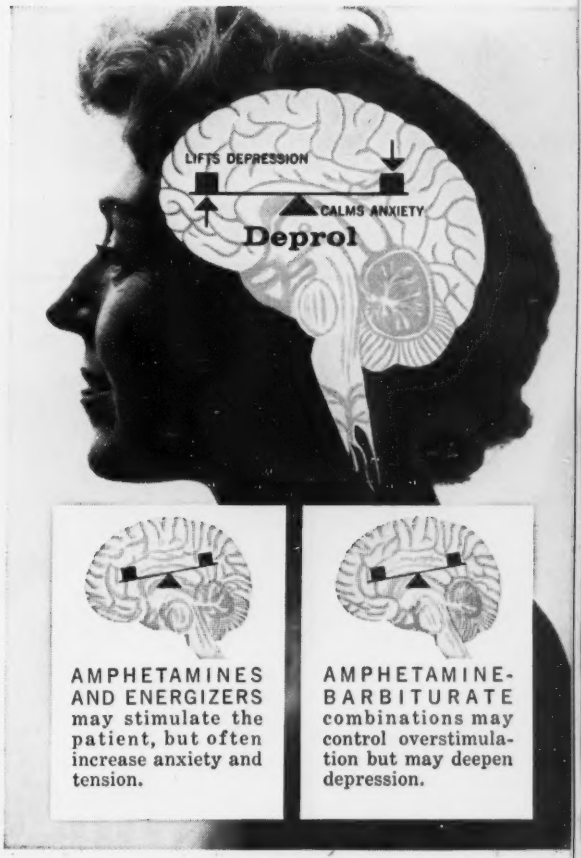
Smooth, balanced action lifts depression as it calms anxiety... swiftly and safely

Balances the mood – no "seesaw" effect of amphetamine-barbiturates and energizers. While amphetamines and energizers may stimulate the patient – *they often aggravate anxiety and tension.* And although amphetamine-barbiturate combinations may counteract excessive stimulation – *they often deepen depression.*

In contrast to such "seesaw" effects, Deprol lifts depression as it calms anxiety – both at the same time.

Acts swiftly – the patient often feels better within a few days. Unlike the delayed action of other drugs which may take two to six weeks to bring results, Deprol's smooth, immediate action relieves the patient quickly – often within a few days.

Acts safely – no danger of liver damage. Deprol does not produce liver damage, hypotension, psychotic reactions or changes in sexual function – frequently reported with other drugs.


LIFTS DEPRESSION
CALMS ANXIETY
Deprol
AMPHETAMINES AND ENERGIZERS may stimulate the patient, but often increase anxiety and tension.
AMPHETAMINE-BARBITURATE combinations may control overstimulation but may deepen depression.

BIBLIOGRAPHY ***(10 clinical studies, 714 patients):***

1. Alexander, L. (35 patients): Chemotherapy of depression – Use of meprobamate combined with benactyzine (2-diethylaminoethyl benzilate) hydrochloride. J.A.M.A. 166:1019, March 1, 1958. **2.** Bateman, J. C. and Carlton, H. M. (50 patients): Meprobamate and benactyzine hydrochloride (Deprol) as adjunctive therapy for patients with advanced cancer. Antibiotic Med. & Clin. Therapy 6:648, Nov. 1959. **3.** Bell, J. L., Tauber, H., Santy, A. and Pulito, F. (77 patients): Treatment of depressive states in office practice. Dis. Nerv. System 20:263, June 1959. **4.** Breitner, C. (31 patients): On mental depressions. Dis. Nerv. System 20:142, (Section Two), May 1959. **5.** McClure, C. W., Papas, P. N., Speare, G. S., Palmer, E., Slattery, J. J., Konefal, S. H., Henken, B. S., Wood, C. A. and Ceresia, G. B. (128 patients): Treatment of depression–New technics and therapy. Am. Pract. & Digest Treat. 10:1525, Sept. 1959. **6.** Pennington, V. M. (135 patients): Meprobamate-benactyzine (Deprol) in the treatment of chronic brain syndrome, schizophrenia and senility. J. Am. Geriatrics Soc. 7:656, Aug. 1959. **7.** Rickels, K. and Ewing, J. H. (35 patients): Deprol in depressive conditions. Dis. Nerv. System 20:364, (Section One), Aug. 1959. **8.** Ruchwarger, A. (87 patients): Use of Deprol (meprobamate combined with benactyzine hydrochloride) in the office treatment of depression. M. Ann. District of Columbia 28:438, Aug. 1959. **9.** Settel, E. (52 patients): Treatment of depression in the elderly with a meprobamate-benactyzine hydrochloride combination. Antibiotic Med. & Clin. Therapy. In press, 1959. **10.** Spiitter, S. R. (84 patients): The care of the anxious and the depressed. Submitted for publication, 1959.

Dosage: Usual starting dose is 1 tablet q.i.d. When necessary, this may be gradually increased up to 3 tablets q.i.d.

Composition: 1 mg. 2-diethylaminoethyl benzilate hydrochloride (benactyzine HCl) and 400 mg. meprobamate.

Supplied: Bottles of 50 light-pink, scored tablets. Write for literature and samples.

▲Deprol▲®

WALLACE LABORATORIES / *New Brunswick, N. J.*

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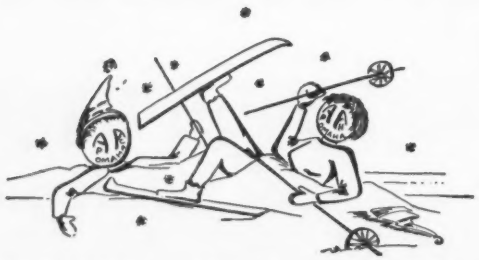

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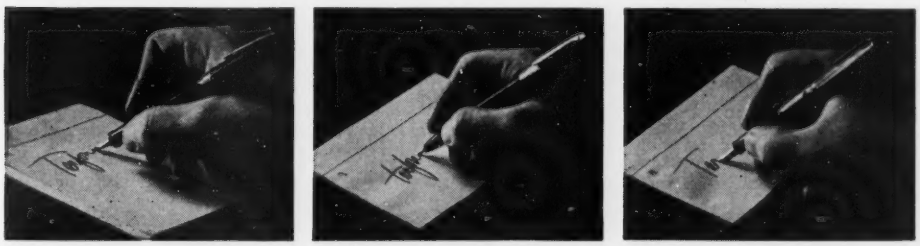

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Squibb Triple Sulfas (Trisulfapyrimidines)

Clinical experience continues to prove that TERFONYL provides many special advantages fundamental to successful antibacterial therapy.

• specificity for a wide range of organisms • superinfection rarely encountered • soluble in urine through entire physiologic pH range • minimal disturbance of intestinal flora • excellent diffusion throughout tissues • readily crosses blood-brain barrier • sustained therapeutic blood levels • extremely low incidence of sensitization

SUPPLY: Tablets, 0.5 gm. • Suspension, raspberry flavored, 0.5 gm. per teaspoonful (5cc.).

SQUIBB *Squibb Quality—the Priceless Ingredient*

"TERFONYL"® IS A SQUIBB TRADEMARK

Tetracycline Phosphate Complex (TETREX®)
U.S. PAT. NO. 2,791,609

in the Therapy of

ACUTE PHARYNGITIS, ESPECIALLY WITH LYMPHADENITIS

Ideally, selection of the proper antibiotic for treatment of acute pharyngitis should await the laboratory reports on the susceptibility of the infecting bacteria. But the busy practitioner who sees many patients a day during the upper respiratory infection season may sometimes find it difficult to avoid the empirical choice of an antibiotic. Unfortunately, this practice may sometimes result in therapeutic failure.

No matter what the pressure of the immediate situation, it is worthwhile to consider taking a bacterial specimen from the infected pharynx for culture and sensitivity studies before starting treatment. Thus, a rational basis will be provided for changing the antibiotic should the first choice prove ineffective.

Which Antibiotic?

All other things being equal, the drug of choice is the one to which the pathogen is most susceptible. But if the exigencies of the situation force the physician to a prompt use of antibiotic, a broad-spectrum preparation that produces immediate high blood levels (e.g., tetracycline phosphate complex, TETREX) probably has the best chance of controlling the pathogen.

Later, the laboratory report frequently may indicate that any one of several antibiotic agents would be equally effective against the particular microorganism in question. In such a case other factors such as frequency and severity of side effects, sensitizing potential and toxicity should be considered.

If the acute pharyngitis in question should be due to gram-negative Klebsiella[1], penicillin will be of no value, nor will erythromycin be effective. However, this organism is susceptible to tetracycline. If the pathogen should turn out to be gram-positive Streptococcus or Staphylococcus, then penicillin, erythromycin, and tetracycline may all be effective against it.

Penicillin, however, in addition to having a limited spectrum, also causes many minor and some serious sensitivity reactions. In a recent survey[2] it was found that penicillin produced severe skin reactions. But most important was the observation that anaphylactic shock, with a fatality rate of about 9 per cent, was the most frequent serious reaction. Such severe reactions are almost always associated with parenteral administration.

The tetracyclines (e.g., TETREX) have the advantages of a broad range of antimicrobial activity and low toxicity. And in addition, the physician does not have to trouble himself or his patients with repeated blood studies when he prescribes TETREX. Minor reactions such as gastric upsets or mild skin rashes occur occasionally. The most serious side effects are staphylococcal and monilial overgrowth, but these are rare and can be adequately controlled.

Some Microorganisms Susceptible[a] to Tetracycline **(TETREX)[b]**

Streptococcus; Staphylococcus; Pneumococcus; Gonococcus; Meningococcus; *C. diphtheriae; B. anthracis; E. coli;* Proteus; *A. aerogenes; K. pneumoniae;* Shigella; Brucella; *P. tularensis; H. influenzae; T. pallidum;* Rickettsiae; Viruses of psittacosis and ornithosis, lymphogranuloma inguinale, primary atypical pneumonia; *E. histolytica; D. granulomatosis.*

[a] Some strains are not susceptible.

[b] Table adapted from Goodman, L. S., and Gilman, A.: The Pharmaceutical Basis of Therapeutics, 2nd edition, New York, The Macmillan Co., 1956, pp. 1322-1323.

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References: 1. Zinsser, H.: A Textbook of Bacteriology. 11th edition, New York, Appleton-Century-Crofts, 1957, p. 409. 2. Welch, H.: Lewis, C. H.; Weinstein, H. I., and Boeckman, B. B.: Severe reactions to antibiotics. A nationwide survey. Antibiotic Med. & Clin. Ther. 4:800 (December) 1957.

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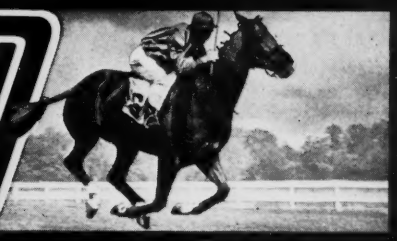

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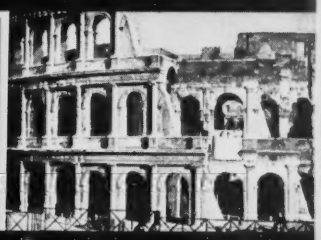

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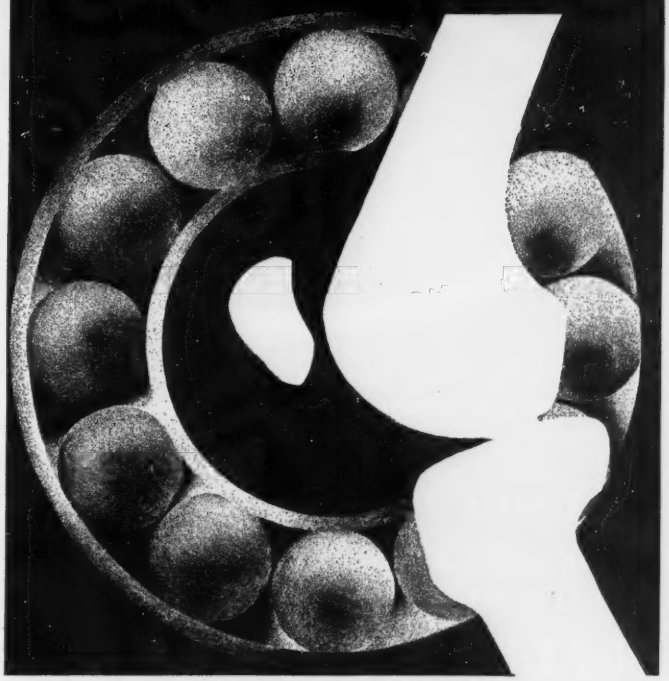

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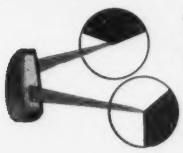

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1. Fabricant, N. D.: E.E.N.T. Monthly *37*:460 (July) 1958.
2. Lhotka, F. M.: Illinois M. J.: *112*:259 (Dec.) 1957.
3. Farmer, D. F.: Clin. Med. *5*:1183 (Sept.) 1958.

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2. Rinehart, R.E., and Marcus, H.: Incidence of Amebiasis in Healthy Individuals, Clinic Patients and Those with Rheumatoid Arthritis, Northwest Med., *54*:708 (July, 1955).

3. Webster, B.H.: Amebiasis, a Disease of Multiple Manifestations, Am. Pract. and Dig. of Treat. *9*:897 (June, 1958).

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Polyphagia	28	25.4
Anorexia	16	14.5
Lethargy	14	12.7
Enuresis	7	6.4
Vomiting	5	4.5
Irritability	3	2.7
"Craving for sweets"	3	2.7
"Sticky diaper"	3	2.7
"Strong odor to urine"	2	1.8
Glycosuria	2	1.8
Hypoglycemia	2	1.8
Personality change	1	0.9
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1. Goddard, E.S.: in *Trifluoperazine, Further Clinical and Laboratory Studies*, Philadelphia, Lea & Febiger, 1959.

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